

An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)_†

Influenza Vaccine Effectiveness, Immunogenicity,
and Safety in Healthy Adults 19-64 Years Old

PROTECTING CANADIANS FROM ILLNESS



Public Health
Agency of Canada

Agence de la santé
publique du Canada

Canada

**TO PROMOTE AND PROTECT THE HEALTH OF CANADIANS THROUGH LEADERSHIP, PARTNERSHIP,
INNOVATION AND ACTION IN PUBLIC HEALTH.**

—Public Health Agency of Canada

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Efficacité, immunogénicité et innocuité des vaccins antigrippaux chez des adultes en santé âgés de 19 à 64 ans

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PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (hereafter referred to as the Agency) with ongoing and timely medical, scientific, and public health advice relating to immunization. The Agency acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and is disseminating this document for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph(s). Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) of the Canadian manufacturer(s) of the vaccine(s). Manufacturer(s) have sought approval of the vaccine(s) and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of the Agency's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

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I. INTRODUCTION

Healthy adults, 19 to 64 years of age, are not at high risk for influenza-related complications; however, they are capable of transmitting disease to those at high risk of complications including the very young, older adults, and those whose immune systems are compromised; all of whom are less capable of mounting an adequate immune response to vaccination than healthy adults and children.

To inform the decision on whether to recommend vaccination for healthy adults, a review of the literature was conducted for adults, 19 to 64 years old, who have no underlying medical conditions (e.g., chronic diseases or infections), and who are not pregnant. Studies are included if less than about ten percent of the participants are outside those specifications. If the study included participants outside of the target population and sub-group analyses were provided for the target population, only that data was abstracted and presented. Studies include those of licensed trivalent inactivated influenza vaccines from manufacturers approved to sell vaccines in Canada (both intramuscular [IM] and intradermal [ID] formulations) and licensed live-attenuated influenza vaccines from all manufacturers. Studies of monovalent 2009 pandemic vaccines and of the burden of disease during the 2009-10 pandemic are excluded from this review. The literature search was conducted using the Medline, Embase, and Web of Science databases for January 1, 2000 to February 2013, the Cochrane database, and the reference lists of key articles (e.g., reviews).

The work includes a review of the burden of disease in healthy adults, with a focus on Canadian statistics, as well as influenza vaccine efficacy and effectiveness, immunogenicity, and safety for the target population and vaccines.

II. BURDEN OF DISEASE

Influenza is ranked among the top 10 infectious diseases affecting the Canadian population ⁽¹⁾. However, due to the variability of the burden of disease from one season to the next, and the ambiguity of symptoms of infection, estimates of the incidence of infection, rates of health care utilization, and mortality vary significantly. These variations depend on the season, which is affected by the virulence of the circulating strain(s) and the proportion of people in the population who are susceptible – which, in turn, is influenced by the percentage of the population who is vaccinated and by vaccine effectiveness. Estimates are also shaped by definitions of the outcome, laboratory tests performed, and the population at risk.

Influenza infections, even those that are symptomatic, are difficult to differentiate from other acute respiratory viral infections. Most healthy adults do not seek medical care for influenza-like illnesses and those who do seek medical care are often not swabbed to determine the cause of illness. Thus, we cannot rely on surveillance of routinely collected data to estimate the burden of disease. A meta-analysis ⁽²⁾, using data from observational studies and randomized trials, estimated that the incidence of influenza in working-aged adults ranges from 1.2% (95% CI [0.9, 1.7]) for those who were vaccinated to 9% (95% CI [6, 14]) for those who were unvaccinated. The highest incidence was reported for unvaccinated adults exposed to children (95% CI [24%, 39%]). The median attack rates for PCR and/or culture-confirmed influenza from blinded randomized controlled trials reviewed for this report were about 2% for people vaccinated with trivalent inactivated influenza vaccine and 5% for unvaccinated participants ⁽³⁾⁻⁽¹⁰⁾. Even the estimates provided from these studies may underestimate the true burden of disease as

participants make judgements about whether the illness is influenza and may forget or decline to provide swabs even with active follow-up. However, they provide the least biased estimate of the true burden of illness caused by influenza in healthy adults.

Not all people with influenza seek medical attention for their illness, with the propensity to seek care dependent upon the severity and duration of symptoms, underlying health conditions, and other factors. Using administrative data from Canadian sources, an average of 3.0% of adults 20-49 years old and 4.0% of adults 50-64 years old visited a physician's office or emergency room annually for pneumonia- or influenza-related illnesses between 1997 and 2004 ⁽¹¹⁾. An estimated 2.3% (95% CI [2.2, 2.3]) of Winnipeg residents 15-64 years of age visited a physician's office and 0.04% (95% CI [0.03, 0.05]) visited an emergency room for pneumonia- or influenza-related illnesses that were in 'excess' of the baseline number of visits estimated for non-influenza periods - during four influenza seasons: 1995-96 to 1998-99 ⁽¹²⁾.

The number of Canadian adults hospitalized for influenza-related illness also varies considerably based on the source of data. The Toronto Invasive Bacterial Diseases Network, a network of acute care hospitals in Toronto and area, reported that there were 1.2 and 4.9 hospital admissions per 100,000 people aged 15-39 and 40-64, respectively, for people with laboratory-confirmed influenza in 2004-05 ⁽¹³⁾. Not unexpectedly, 47% of 15-39 year olds and 62% of 40-64 year old adults hospitalized during this study had a chronic underlying disease, which is higher than expected for the general population. These estimates are much lower than the average reported by reviewing hospital discharge data for Canada where an average of 93 and 313 hospital stays annually per 100,000 Canadians aged 20-49 and 50-64 years, respectively, were attributable to influenza or pneumonia for 1997-98 through 2003-04 ⁽¹¹⁾.

The mortality rate due to influenza is much lower for adults 19-64 years of age than it is for very young children or people 65 years and older. In a Canadian study looking at causes of death for 1989-90 through 1998-99, an average of 307 deaths annually were 'certified' as being caused by influenza ⁽¹⁴⁾. However, according to these authors, more than 60% of the deaths that should have been attributed to influenza were certified as heart diseases, pneumonia, or chronic obstructive pulmonary disease. They estimate that an average of 4,000 deaths per year (ranging from close to 0 to 8000 annually) were attributable to influenza. Of these, about 150-160 deaths due to influenza occur every year in adults 50 to 64 years of age (about 1.8 per 100,000), with significantly fewer deaths in younger adults ⁽¹⁴⁾. In the USA, the estimated mortality rate associated with influenza is 1.5 (95% CI [0.4, 3.1]) per 100,000 in people 19-64 years old ⁽¹⁵⁾.

III. VACCINE EFFICACY AND EFFECTIVENESS

Vaccine efficacy (estimates of how effective the vaccine is at preventing infection under ideal circumstances, e.g. study conditions) and effectiveness (how successful the vaccine is at preventing infection under real-world conditions) vary with the capability of the individual's immune system (often affected by age, chronic diseases, medications, etc.), the match between the vaccine and circulating strains of virus, how efficacy/effectiveness is measured (laboratory-confirmed versus influenza-like illness), the laboratory test used (polymerase chain reaction versus culture), and the definition of illness, and the vaccine itself (trivalent inactivated versus live attenuated). This report describes the efficacy and effectiveness of vaccines manufactured by companies that provide influenza vaccines in Canada separately for laboratory-confirmed infections and influenza-like illnesses, for trivalent inactivated and live attenuate vaccines, and by study type.

III.1 Laboratory-confirmed infection

Illnesses caused by the influenza viruses vary in their symptoms and course of illness. Thus, vaccine efficacy and effectiveness estimates based on laboratory-confirmed infection are less biased than estimates based on outcomes such as influenza-like illness. Randomized controlled trials, using placebo injections are the 'gold standard' since underlying differences between people who chose to be vaccinated or not are eliminated and because they are less likely to be biased by participant and/or researcher expectations of protection through vaccination than other types of studies. Real time polymerase chain reaction laboratory tests are the current standard for detecting influenza virus from samples (nasopharyngeal, nasal, throat, etc.) since they are more sensitive than culture-based tests. Both PCR and culture tests are more sensitive than rapid antigen tests.

III.1.1 Trivalent inactivated influenza vaccine

Eleven randomized controlled trials (RCT) estimated vaccine efficacy for intramuscularly-administered (IM) trivalent inactivated influenza vaccines (TIV) using laboratory-confirmed influenza as the outcome. Six of these articles used a combination of polymerase chain reaction (PCR) and culture-confirmed influenza to define infection⁽³⁾⁽⁵⁾⁻⁽⁸⁾⁽¹⁰⁾. The other five articles used only one method to confirm diagnosis. Three articles in this group are from the same research group, Ohmit, Monto et al., who authored papers with results from three influenza seasons (2004-05, 2005-06, and 2007-08) with healthy adults (18-64 years old) living in Michigan. The other three articles are from different research groups, with adult participants from Europe, the USA, and Canada. These six studies involved almost 11000 healthy community-based adults who were randomly assigned to receive TIV and over 7000 who received placebo or, in one study, antiviral prophylaxis. All participants were actively followed throughout each influenza season and were swabbed using nasopharyngeal, nasal, and/or throat swabs when they reported influenza-like illnesses. All studies were conducted from 2004-05 through 2007-08. One study estimated relative effectiveness of TIV to antiviral prophylaxis at 30%. The effectiveness of antiviral prophylaxis was lower than expected because the 5 participants in this small pilot study contracted influenza *before* prophylaxis was initiated⁽⁸⁾. Vaccine efficacy estimates for the placebo controlled studies ranged from 16% (95% CI [-171, 70]) in 2005-06 in the USA, a season with a low attack rate (1.5, 1.8%) and a mismatch between the vaccine and circulating influenza B strain⁽⁵⁾, to 75% (95% CI [42, 90]) in 2003-04, a season with higher attack rates and a mismatch between the vaccine and circulating strain of A/H3N2⁽⁶⁾. The other three RCTs had similar estimates of efficacy: 55% (95% CI [41, 65]) in 2006-07 in European countries⁽¹⁰⁾ and 63% (95% CI [47, 79]) and 68% (95% CI [46, 81]) for studies done in 2007-08 in the USA and Europe⁽³⁾ and the USA⁽⁷⁾, respectively.

Although attack rates are somewhat lower when using culture only compared to culture combined with PCR or PCR alone, estimates of vaccine efficacy are similar. Three RCTs were reviewed that used only culture-based methods to test for influenza infection of nasal and/or throat swabs when participants reported an influenza-like illness during active follow-up⁽¹⁶⁾⁻⁽¹⁸⁾. These studies involved over 13000 vaccinated and almost 9000 unvaccinated participants and were conducted from 2005-06 through 2007-08. The lowest estimate of vaccine efficacy was 22.3% (95% CI [-49, 59]) in 2005-06 in Europe, a season with low attack rates (1.0-2.3%) in healthy adults⁽¹⁸⁾, the same year with the low efficacy estimates noted above. Two other articles estimated vaccine efficacy at 49% (95% CI [20, 70]) for a study done in the USA in 2005-06 and 2006-07⁽¹⁶⁾ and 62% (95% CI [46, 73]) for a study done in 2006-07 in Europe⁽¹⁷⁾. The results of one study are reported twice, in two different articles, in this section. They confirm the similarity

in estimates of vaccine efficacy using either culture-confirmed or PCR: vaccine efficacy for influenza was estimated as 54.7% (95%CI [40.7, 65.4]) by rtPCR (culture positive or negative) and 61.6% (95%CI [46.0, 72.8]) by culture irrespective of match to vaccine strain⁽¹⁰⁾⁽¹⁸⁾.

Six test-negative case-control studies estimated vaccine effectiveness in healthy adults. These studies are based on patients who self-refer to sentinel physicians for influenza-like complaints. Physicians then decide whether or not to test for influenza. All used PCR to test for influenza infection. Although age and known underlying medical conditions are often controlled for in the calculation of vaccine effectiveness, unknown confounders and effect modifiers likely affect the estimates. In a Canadian study conducted in 2005-06, sentinel physicians tested 201 adults aged 20-64 years old without chronic conditions. In this test-negative study, the unadjusted effectiveness of TIV was estimated at 22% (95% CI [-5, 49]) in 2005-06, a year with low vaccine efficacy estimates as noted above⁽¹⁹⁾. Similar studies conducted in Australia and in Europe showed, after adjusting for confounders, an estimated effectiveness of 54% (95% CI [7, 77])⁽²⁰⁾ and an estimated effectiveness of 61% (95% CI [-3, 85])⁽²¹⁾ respectively. One study estimated effectiveness, adjusted for co-morbidities and month of swab collection, at 35% (95% CI [-56, 73]) in 2007-08 and at 64% (95% CI [29, 82]) in 2006-07⁽²²⁾. Vaccine effectiveness in USA military personnel who consulted a healthcare provider for influenza-like illnesses in 2010-11 was estimated at 53% (95% CI [25, 71]) when comparing test-negative controls with cases. When comparing test-positive cases with healthy controls (military personnel consulting for musculoskeletal complaints), vaccine effectiveness was estimated at 21% (95% CI [-1, 42]), not significantly different than when comparing test-negative controls⁽²³⁾.

Estimates from cohort studies, like case-control studies, are based on participants who chose whether or not to be vaccinated. However, the participants are enrolled before the influenza season starts and actively followed throughout the season to determine whether they become infected. A cohort study that followed 1374 military recruits in Finland estimated vaccine effectiveness during an outbreak of influenza during the 1997-98 season at 57% (95% CI [40, 68])⁽²⁴⁾. Meanwhile, a cohort study using rapid antigen tests to diagnose influenza in Japanese hospital workers estimated vaccine effectiveness at 60% during the 2002-03 season⁽²⁵⁾. Neither of these estimates is significantly different than those from RCTs or test-negative case control studies.

III.1.2 Live attenuated influenza vaccine

Ohmit, Monto et al. studied the efficacy of live attenuated influenza vaccine (LAIV) in three RCTs, all of which also studied the efficacy of TIV. Almost 2500 healthy adults vaccinated with LAIV were compared with almost 1000 adults given placebo. Vaccine effectiveness estimates ranged from 7.5% (95% CI [-194, 67]) in the 2005-06 season with low attack rates and low efficacy estimates for TIV⁽⁶⁾ to 48% (95% CI [-7, 74]) in the 2004-05 influenza season⁽⁶⁾. In 2007-08 season, the estimated efficacy of LAIV was 36% (95% CI [0-59]) in healthy adults living in the USA⁽⁷⁾.

A case-control study conducted with USA military personnel in 2010-11 estimated vaccine effectiveness for LAIV at -13% (95% CI [-77, 27]) compared with personnel who had an ILI but tested negative for influenza and 11% (95% CI [15, 31]) compared with personnel who consulted a physician for musculoskeletal complaints⁽²³⁾.

III.1.3 Relative efficacy: Trivalent inactivated¹ versus live attenuated influenza vaccines

Three RCTs conducted by Ohmit, Monto et al. compared the relative efficacy of TIV to LAIV in healthy adults. In the 2003-04 season, there was an estimated 53% (95% CI [-5, 80]) reduction in laboratory-confirmed influenza, a 9% (95% CI [-110, 60]) reduction in 2005-06, and a 50% (95% CI [20, 69]) reduction in 2006-07 for people receiving TIV over those receiving LAIV⁽⁵⁾⁻⁽⁷⁾. Eick-Cost et al. also found that TIV was more effective than LAIV for preventing influenza in healthy military personnel with a relative reduction of 27%⁽²⁶⁾ in laboratory-confirmed influenza for personnel vaccinated with TIV compared with those vaccinated with LAIV using negative controls, and a reduction of 13% when comparing cases to controls visiting for musculoskeletal complaints⁽²³⁾.

Summary of vaccine efficacy estimates against laboratory confirmed influenza:

Vaccine efficacy estimates against laboratory confirmed influenza for TIV in healthy adults 18-64 years of age range widely from as low as 15% to as high as 75%. However, the majority of the seasons and populations studied have efficacy estimates of 50-60%. Estimates appear to depend on the year of the study, which likely reflects the virulence of the strain and how well the vaccine was matched with the circulating strains of influenza. Efficacy estimates for military recruits are not significantly different than for healthy adults living in the community and rates in Europe and Australia are similar to those reported in Canada and the USA. Vaccine efficacy for LAIV was lower than for TIV in all four RCTs that compared them directly.

III.2 Influenza-like illness

Influenza infections, even those that are symptomatic, are difficult to differentiate from other acute respiratory viral infections. In three studies reviewed for this report, 13-22% of people with an ILI tested positive for influenza⁽¹⁰⁾⁽¹⁷⁾⁽¹⁹⁾ making ILI an inadequate proxy of influenza infection.

III.2.1 Trivalent inactivated influenza vaccine

Six RCTs evaluated vaccine efficacy for TIV in healthy adults using ILI as the outcome. Five of the six studies used the Center for Disease Control and Prevention (CDC) definition of an ILI to prompt participants to visit the clinic or study office to have a nasal, nasopharyngeal, or throat sample collected. The CDC definition is a fever *and* cough and/or sore throat (in the absence of a known cause other than influenza). The other study defined an ILI at least one systemic and one respiratory symptom⁽¹⁰⁾. Vaccine efficacy, using ILI as the outcome, was negative in three studies⁽¹⁷⁾⁽²⁷⁾⁽²⁸⁾ indicating that influenza vaccine did not confer protection against ILI. However, one of these studies had a vaccine efficacy estimate of 22% (95% CI [-49, 59])⁽¹⁷⁾ when using PCR-confirmed infection as the outcome indicating that the vaccine was effective in preventing actual infection. The other four studies did have a positive vaccine efficacy, but none that reached the efficacy reported in the majority of RCTs using influenza infection as the outcome. The vaccine effectiveness estimates using ILI as the outcome were 14% (95% CI [7, 20]) in 1996-97⁽²⁹⁾, 19% in 2006-07⁽¹⁰⁾, 27% in 2007-08⁽³⁾, and 34%⁽²⁸⁾ in the 1998-99 influenza seasons.

Five cohort studies spanning the influenza seasons of 1997-98 through 2006-07 also estimated vaccine effectiveness for TIV using ILI as the outcome. These studies were conducted with the USA military⁽³⁰⁾, Finish military⁽²⁴⁾, in Taiwan⁽³¹⁾, Malaysia⁽³²⁾, Russia⁽³³⁾, and France⁽³⁴⁾. Estimates of effectiveness based on physician consultations were negative and zero⁽³¹⁾ for a study conducted in 1997-98 and 1998-99 in a Taiwanese workplace. Similarly low rates of effectiveness (-5% and 7%) were reported for a study of general practitioners in Belgium in 2002-03 and 2003-04⁽³⁵⁾ who self-reported ILI. University students involved in a four-year cohort study in the USA had an estimated effectiveness of 18%⁽³⁶⁾, similar to the effectiveness based on low-risk patients visiting physicians for ILI in the United Kingdom from 1996-97 through 2006-07: 23 and 25% for people 50-69 years old and 20-49 years old, respectively⁽³⁷⁾. Rates of effectiveness were 33% (95% CI [26-40]) in 2005-06 and again in 2006-07 compared with 54% (95% CI [50-57]) in 2003-04 in a three year study conducted in the USA military⁽³⁰⁾. A second study of military personnel reported a vaccine effectiveness estimate of 53% (95% CI [41, 63]) for a study conducted in 1997-98 in Finland⁽²⁴⁾. A similar rate of effectiveness, 48% (95% CI [27, 86]) was estimated in a cohort study of people 50-64 years old working at a university in the USA in 2006-07⁽³⁸⁾. In comparison, estimates based on active follow-up of workers in Malaysia and Russia estimated effectiveness at 70-73%⁽³²⁾⁽³³⁾.

III.2.2 Trivalent inactivated influenza vaccine

One study estimated the effectiveness of LAIV in healthy adults over three seasons using ILI as their outcome. Estimates for passive follow-up via healthcare provider visits, adjusted for age, sex, medical background, and service branch ranged from 6% (95% CI [-9, 19]) to 12% (95% CI [0.8, 21])⁽³⁰⁾, lower than the estimates for TIV effectiveness from the same study; TIV effectiveness estimates were 33% (95% CI [26, 40]) to 54% (95% CI [50, 57]).

III.2.3 Relative effectiveness: Trivalent inactivated versus live attenuated influenza vaccines

Two studies compared the relative effectiveness of TIV and LAIV using healthcare encounters for ILI as the outcome. There was no difference in TIV and LAIV effectiveness in one comparison of USA military personnel visiting a healthcare provider during the influenza seasons of 2006-07 through 2008-09 when the ILI definition was broad and included ICD-9 codes for ILI complaints. However, when the definition was restricted to physician diagnosis of influenza, there was a 20% reduction in ILI for TIV compared with LAIV⁽³⁹⁾. There was also a 13-32% reduction in ILI for TIV compared with LAIV for military personnel followed for the 2004-05 through 2006-07 influenza seasons⁽³⁰⁾.

Summary of vaccine effectiveness against influenza-like illness

Estimates of vaccine effectiveness are less reliable when using ILI as the outcome compared with laboratory-confirmed influenza. Nevertheless, effectiveness estimates based on ILI range from no protective effect to as high as 73% for TIV. As seen with laboratory-confirmed influenza infection, effectiveness of LAIV against ILI was shown to be somewhat lower than the effectiveness of TIV in healthy adult population.

IV. IMMUNOGENICITY

Immunogenicity against the three strains included in influenza vaccines is typically measured by comparing the pre-vaccination and post-vaccination hemagglutinin inhibition (HI) antibody titres, usually 21-28 days after vaccination. However, the measurement of HI titres varies from one laboratory to another which makes comparisons problematic although recent attempts to standardize methods may have ameliorated this problem.

All TIVs approved for use in healthy adults in Canada use 15 µg per strain for intramuscular and 9µg per strain for intradermal injections. Only vaccines meeting these requirements are reviewed here. The association between protection against influenza infection after vaccination with LAIV is not closely associated with HI antibody titres from serum. However, available data on HI titre analyses is reviewed. Data is presented by age group when available.

IV.1 Seroprotection

A common measure of immunogenicity is seroprotection, defined by the Committee for Proprietary Medicinal Products (CPMP) as having a HI titre of $\geq 1:40$ ⁽⁴⁰⁾. It is suggested that HI antibody titres $\geq 1:40$ may be associated with a 50% reduction in infection⁽⁴¹⁾.

IV.1.1 Trivalent inactivated influenza vaccine

The rate of seroprotection against the A/H1N1 component contained in TIV administered intramuscularly to healthy adults 19 to 64 years of age have overlapping confidence intervals, with a low estimate of 82% (95% CI [60, 95])⁽⁴²⁾ and a high estimate of 100% (95% CI [95, 100])⁽⁴³⁾. Seroprotection against the A/H3N2 component ranges from 63% (95% CI [51, 75])⁽⁴²⁾ to 100% (95% CI [95, 100])⁽⁴³⁾⁽⁴⁴⁾. Seroprotection against the influenza B components of vaccines is somewhat lower than that against the A strains in some, but not all, of the studies and rates range from 56% (95% CI [50, 61])⁽⁴⁵⁾ to 100% (95% CI [95, 100])⁽⁴³⁾.

Participants 19 to 49 years of age tend to have a somewhat higher rate of seroprotection than people 50 to 64 years old. Two studies compared seroprotective rates in these age groups. No differences in rates of seroprotection against the A/H1N1 or A/H3N2 components were noted in either study. However, seroprotection against the B components were higher for younger people in both studies: 82% (95% CI [78, 87]) for 18-49 year olds compared to 71% (95% CI [65, 76]) for 50 to 64 year olds⁽⁴⁶⁾ and 88% (95% CI [83, 92]) compared to 74% (95% CI [68, 80]), respectively⁽⁴⁷⁾. No differences were noted in the rates of seroprotection by vaccine manufacturer or brand name.

One study vaccinated the same participants each year for three years and assessed the immunogenicity for each year. The participants were randomized to receive either Vaxigrip or an investigational intradermal vaccine the first year. In the second year, those who received Vaxigrip were vaccinated with the intradermal vaccine and vice versa. For the third and final year, the participants received their vaccine by the same route as in the first year of the study. Focusing only on the HI antibody response for those receiving the Vaxigrip TIV in year one and three, rates of seroprotection increased or were stable from year one through year three. For example, the A/H1N1 component in all three years (2003-04 through 2005-06) was A/New Caledonia/20/1999. The proportion of the participants who received Vaxigrip in years one and three that were seroprotected was 87% (95% CI [83, 90]) in the first year, 93% (95% CI [90, 95])

in the second and 91% (95% CI [84, 96]) in the third year of the study. The same pattern was noted for both the A/H3N2 and B strains even though the strains changed every year of the study⁽⁴⁵⁾.

Intradermal TIV uses a less antigen per strain (9µg) than intramuscular formulations (15µg), yet induces a similar level of seroprotection. In the two studies that report rates of seroprotection for adults 19-64 years old, 90-100% of participants were seroprotected to all three components following vaccination⁽⁴⁸⁾⁽⁴⁹⁾. In a study that compared seroprotective rates by age group, younger adults (18-49 years old) had higher rates of seroprotection than participants 50 to 64 years of age, with statistically significant differences for two of the three vaccine components: 89% (95%

CI [85, 93]) vs. 72% (95% CI [65, 78]), respectively for A/H1N1 and 85% (95% CI [79, 89]) vs. 67% (95% CI [60, 73]), respectively for influenza B. Seroprotection against the A/H3N2 strain was similar for both age groups⁽⁴⁷⁾.

IV.1.2 Live attenuated influenza vaccine

LAIV does not induce a strong HI antibody response in adults. One small (N=39) RCT compared the seroprotection response in younger adults (20-49 years old) who, following LAIV administration, ingested either a *Lactobacillus* probiotic capsule or a placebo twice daily. These authors reported HI titres of greater than or equal to 1:40 for 37% and 45%, 58% and 40%, and 37% and 25%, for the A/H1N1, A/H3N2, and B strains in people receiving the probiotic and placebo, respectively⁽⁵⁰⁾.

Summary: Seroprotection

Rates of seroprotection, as measured by HI antibody titres, against the three strains of influenza virus included in each year's vaccine are slightly higher for younger adults (19-49 years old) than people 50-64 years old. Intradermal administration appears to induce seroprotective levels of antibodies in a similar proportion of vaccinees as IM administered vaccines. LAIV does not induce the same serological response as injected vaccines although it is shown to be nearly as efficacious in protecting against infection.

IV.2 Seroconversion

A second measure of immunogenicity is seroconversion. It is defined as a four-fold or greater increase in pre- and post-vaccination titres or an increase from <1:10 to 1:40⁽⁴⁰⁾. People previously vaccinated or infected with the same strain of influenza may have a higher baseline HI antibody titre and be less likely to seroconvert yet may still be seroprotected (HI titre ≥1:40).

IV.2.1 Trivalent inactivated influenza vaccine

The rate of seroconversion to the A/H1N1 component of intramuscularly administered TIV range are as low as 16-20% in adults with histories of previous influenza vaccination⁽⁴⁵⁾⁽⁴⁶⁾⁽⁵¹⁾. Participants in the Engler study had higher rates of seroprotection (39% in those aged 50-64 years and 54% in those aged 18-64)⁽⁴⁶⁾ which may reflect differences in HI laboratory testing methods used in the different studies. In the other two studies, about 90% of participants had seroprotective levels of antibody against the A/H1N1 component of the vaccine. This is likely explained by the fact that they had received the same A/H1N1 strains as part of the annual

vaccine given during the first year⁽⁵¹⁾ and first two years⁽⁴⁵⁾ of the studies. The highest rate of seroconversion to A/H1N1 strains in the studies reviewed was 96% (95% CI [92, 98]) which was in a vaccine naïve (<0.01% had a history of influenza vaccination) population⁽⁵²⁾. Similar rates and patterns of seroconversion are noted in the A/H3N2 and B strains included in the vaccines with lower rates noted in people with previous influenza vaccination histories and higher rates in so-called naïve participants.

Rates of seroconversion for the intradermally administered TIV mirror those reported for the intramuscularly administered TIV (above): lower rates of seroconversion occurred in a population with high rates of previous vaccination and the accompanying rates of seroprotection were 97-100%⁽⁴⁸⁾⁽⁴⁹⁾.

IV.2.2 Live attenuated influenza vaccine

As mentioned earlier, LAIV does not induce the same rates of seroprotection, as measured by HI antibody titres, as the inactivated vaccines. Rates of seroconversion, as defined for TIV, range from 0 to 45% for any of the three vaccine components⁽⁴⁾⁻⁽⁶⁾⁽⁵⁰⁾⁽⁵³⁾⁻⁽⁵⁵⁾. No differences in levels of seroconversion are noted by participant age or whether they had previous influenza vaccination. Although several authors explored other measures of response to LAIV, none of those reviewed provided good alternative measures.

Summary: Seroconversion

Rates of seroconversion for TIV are high for vaccine naïve participants. Lower rates of seroconversion are noted for people with recent influenza vaccinations but they have correspondingly high rates of seroprotection. Rates of HI antibody seroconversion are not reliable estimates of protection against infection for people receiving LAIV.

V. VACCINE SAFETY AND REACTOGENICITY

Vaccine safety is evaluated in several ways. Participants in vaccine trials are often asked to complete diaries detailing any reactions that occur within the first week after vaccination and are asked to report any adverse events, often until the end of the influenza season, and are reported in publications about vaccine efficacy, immunogenicity, and safety. Adverse events following immunization (AEFI) forms may also be submitted to local, regional, and federal government health agencies by healthcare providers or the general public. In Canada, these reports are compiled in the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) and shared with Health Canada. Trials to assess safety issues in special populations (e.g., people with allergy to eggs) are often conducted under close medical supervision. Studies are also conducted on administrative data regarding healthcare provider consultations and/or hospitalizations for specific conditions (e.g., Guillain Barré syndrome) to determine whether there is an association between vaccination and these outcomes.

V.1 Administration site reactions

The most common side effect following IM administration of influenza vaccine is pain, which is reported by 40-60% of healthy adults. Up to 10% of people rate the pain following injection as moderate to severe⁽²⁷⁾⁽⁵²⁾⁽⁵⁶⁾. In blinded studies, the proportion of people noting pain following vaccine administration is significantly higher than for people receiving saline injections⁽³⁾⁽⁵⁾⁻⁽⁷⁾⁽⁵⁷⁾.

A similar proportion, about 37-50%, of participants report pain after receiving influenza vaccine administered intradermally (ID) using the BD microinjection system (provided with the Intanza® vaccines) with 12-13% reporting the pain as moderate to severe⁽⁴⁸⁾⁽⁴⁹⁾.

People receiving ID-TIV are more likely to report redness, swelling, induration, and itching at the site than people receiving IM-TIV. Redness was reported by 74-95% of ID-TIV recipients⁽⁴⁷⁾⁽⁴⁸⁾ compared with 5-30% of people receiving IM-TIV⁽³⁾⁽⁵⁶⁾⁻⁽⁵⁹⁾. Redness also tended to last longer following ID administration; 44% of participants reported redness that lasted 4 or more days compared with 1.3% of people who received IM-TIV⁽⁴⁹⁾. Swelling was reported by 27% of people receiving ID-TIV and 1% of those receiving IM-TIV in one RCT⁽⁴⁷⁾ although up to 68% of people receiving ID-TIV⁽⁴⁸⁾ and up to 22% of people receiving IM-TIV reported swelling in other studies⁽⁵⁶⁾. Induration was reported by 60-70% of ID-TIV recipients compared with 0-27% of IM-TIV recipients⁽⁴⁸⁾⁽⁴⁹⁾⁽⁶⁰⁾. Itching was reported at the injection site of 5-35% of those receiving their TIV by ID compared with 1-7% of those receiving IM-TIV⁽⁴⁵⁾⁽⁴⁷⁾⁽⁴⁹⁾.

Rhinitis, sore throat, and cough in the first 7 days following vaccination are the most common reactions to LAIV and occur significantly more often in participants receiving LAIV than in people receiving saline placebo. In RCTs directly comparing LAIV with saline placebo in blinded studies, rhinitis occurs in 43-52% of LAIV recipients compared with 27-38% of people getting saline. Sore throat occurs in 25-27% of LAIV recipients compared with 16-17% of saline recipients. LAIV is also more likely to cause cough than saline: 13-18% versus 8-11%⁽⁵⁾⁻⁽⁷⁾⁽⁶¹⁾.

V.2 Systemic reactions

Myalgia is a common complaint following vaccination with any of the three formulations available for adults, occurring in 5-30% of vaccinees. However, there are conflicting results about whether the proportion of people reporting myalgia is higher in people receiving vaccine than in those receiving placebo. No RCTs have been conducted in ID-TIV. For IM-TIV, two RCTs⁽⁵⁾⁽⁵⁷⁾ report higher rates of myalgia while two others report no difference compared with those receiving placebo⁽³⁾⁽⁶⁾. Similarly uncertainty is apparent when comparing LAIV with placebo in RCTs; one study reports a higher proportion of participants complaining of myalgia following LAIV⁽⁶⁾ while two other RCTs report no difference⁽⁷⁾⁽⁶¹⁾.

Although it is not unusual for healthy adults to report a headache, fever/feverishness/chills, feeling tired, weak, or unwell (malaise) following receipt of the influenza vaccine, only one RCT reported a higher proportion of participants complaining of headache when people were blinded to LAIV or saline placebo, ⁽⁶⁾. One RCT reports a higher rate of tiredness (25% versus 21%) following receipt of LAIV than placebo⁽⁶¹⁾. In people receiving IM-TIV, one RCT reports a higher proportion of participants developed a fever following vaccination (3.2% versus 1.6%) compared with those receiving placebo⁽²⁹⁾. No other RCTs report a significant difference in these systemic reactions following vaccination with either IM-TIV or LAIV compared with people receiving a placebo⁽⁵⁾⁽²⁹⁾⁽⁵⁷⁾⁽⁶¹⁾⁽⁶²⁾.

VI. SERIOUS ADVERSE REACTIONS FOLLOWING VACCINATION

Any adverse events that result in death, are life-threatening, require hospitalization (or prolonged length of hospital stay), result in residual disability, or cause congenital anomalies are

considered serious⁽⁶³⁾. The association between vaccination and adverse event need not be causal, but must have a temporal relationship.

Several severe adverse events were reported in the articles reviewed and all possibly-related events are described. Following vaccination with TIV-IM, one recipient complained of chest pain, dyspnea, and headache on the day of vaccination⁽⁶⁴⁾, one person had a spontaneous abortion 2 months after vaccination⁽⁴⁴⁾, and a case of peritonsillar abscess was considered possibly related⁽⁴⁹⁾. Two deaths occurred in another study, one in the group who received vaccine, but neither were considered related to the vaccine⁽³⁾. Following vaccination with LAIV, there was one case of acute pericarditis⁽⁶⁾ and one person was hospitalized with viral meningitis⁽⁵⁾. One case of viral meningitis was also reported in another study, but was not considered related to vaccination⁽⁵⁴⁾.

Authors of a review of adverse events following TIV vaccination of the French armed forces between 2002 and 2010, excluding events linked with the 2009 monovalent influenza vaccine, reported 13.2 events per 100,000 influenza vaccinations. Of these, 0.9 per 100,000 were considered severe including one case of leukoencephalomyelitis three weeks after vaccination. There were also three people with thrombocytopenia 6-10 days following vaccination, two of whom were vaccinated with other vaccines at the same time as their influenza vaccine. One case of hypoglycaemia was reported the day after vaccination, one person had urticaria the day of vaccination, one case of myopericarditis was diagnosed two days after vaccination, and one person had a vasovagal episode the day following vaccination⁽⁶⁵⁾.

The following section of the report is *not* an exhaustive review of the available information. It does focus on the relationship between influenza vaccination and the onset of Guillain-Barré syndrome (GBS). Infectious diseases and various vaccines, including influenza vaccines, have been linked to the onset of GBS. Of note, GBS is more common in adults 65 years and older which is not the age range which is the focus of this review. The following articles include adults 18 years and older and is not an exhaustive review of the literature, so caution in the interpretation of the results is warranted. Not unexpectedly, the evidence is not consistent about the relationship between GBS and the receipt of influenza vaccine.

A time-series (ecological) analysis was conducted on data from the province of Ontario between June 1991 and March 2004 to determine whether there was any change in the incidence of GBS following the institution of the universal influenza vaccination program in 2000⁽⁶⁶⁾. There was an average of 170 hospital admissions due to new cases of GBS annually, with no evidence of seasonality and no trend indicating an increase following universal vaccination. A second analysis, a self-matched case series, was conducted for adults (18 years and older) admitted with GBS between April 1993 and March 2004 who had a record of vaccination in October or November and within 43 weeks prior to their admission (N=269). Adults hospitalized for a new case of GBS were more likely to be admitted 2-7 weeks after influenza vaccination than during a summer control period (26-43 weeks after vaccination) – or for 3 other control periods: 32-43 weeks, 20-43 weeks, or 18-41 weeks after vaccination. The estimated incidence was 1.45 (95% CI [1.05, 1.99]). Of note, this analysis includes adults 18 years and older and the vaccine received was not necessarily for influenza (but limiting it to this age group and months of October and November increases the chances that it was).

A self-controlled case series study was conducted in the United Kingdom using the General Practice Research Database which has over 3 million patients, for 1990 through 2005⁽⁶⁷⁾. The relative incidence of GBS within 90 days of influenza vaccination was 0.76 (95% CI [0.41, 1.40])

indicating no increased risk. In comparison, there was a significant increased risk of GBS within 90 days of a physician visit for ILI (7.3 (95% CI [4.4, 12.4])).

A review of the Vaccine Adverse Events Reporting System (VAERS) in the USA between July 1990 and June 2003 determined that 501 reports of GBS following influenza vaccination occurred in adults 18 years and older with annual rates ranging from 0.04 to 0.17 per 100,000 doses administered⁽⁶⁸⁾. There was a decline in the number of GBS cases reported since the 1996-97 influenza season despite a two-fold increase in influenza vaccination coverage

between 1988-89 and 1999-2000. However, the authors do not rule out a possible association between vaccination and GBS as there was a low proportion of cases with preceding illness (24%) and the median days between vaccination and onset of symptoms was 13.

A review of the Korean National Vaccine Injury Compensation Program between 2003 and 2010 revealed 42 potentially serious adverse events following the distribution of approximately 75 million doses of TIV. The 2009pdm vaccine was not included nor were cases following vaccination programs in 2009. Of the 42 serious events (0.056/100,000 doses), there were 27 neurological events, including 9 GBS cases. The interval between vaccination and GBS was 18 days. The median age for was 55 years for GBS and over 65 years for other neurological events. There were 3 cases of GBS and 7 cases of other neurological events in adults 19-64 years of age, but no estimate of the number of influenza vaccines distributed to people in this age group. People of working age are not a target group for influenza vaccination unless they work in a healthcare setting. After review by the Korean advisory committee, 4 neurological events and 4 GBS cases were considered possibly or likely associated equalling an event rate of 0.005 cases/100,000 doses, per category⁽⁶⁹⁾.

VII. SUMMARY

As burden of disease varies from one season to the next due to such things as changes in the circulating virus strain, the proportion of people in the population who are susceptible, and the number who seek medical attention, estimates of the incidence of infection, rates of health care utilization, and mortality vary significantly. One meta-analysis⁽²⁾ estimated that the incidence of influenza in working-aged adults ranges from 1.2% (95% CI [0.9, 1.7]) for those who were vaccinated to 9% (95% CI [6, 14]) for those who were unvaccinated. The highest incidence was reported for unvaccinated adults exposed to children (95% CI [24% ([15, 39])]). The mortality rate due to influenza is much lower for adults 19-64 years of age than it is for very young children or people 65 years and older.

Estimates of effectiveness vary by type of vaccine (TIV vs. LAIV), by season, and by strain match. Studies that compared the relative efficacy of TIV to LAIV in adults found that TIV was either more effective than LAIV or that the efficacy was comparable in adult recipients of TIV or LAIV. TIV efficacy estimates against laboratory confirmed influenza in healthy adults 18-64 years of age ranged widely from as low as 15% to as high as 75%, with the majority of studies estimating efficacy at 50-60%.

Rates of seroprotection are slightly higher for younger adults (19-49 years old) than for people 50-64 years old. Intradermal administration appears to induce seroprotective levels of antibodies in a similar proportion of vaccinees as IM administered vaccines. LAIV does not induce the same serological response as injected vaccines, which is expected for a mucosal

vaccine. Rates of seroconversion for TIV are high for vaccine naïve participants, with lower rates noted for people with recent influenza vaccinations, but they have correspondingly high rates of seroprotection. Rates of HI antibody seroconversion are not reliable estimates of protection against infection for people receiving LAIV.

Vaccine safety is evaluated in several ways. The most commonly reported side effect following IM administration is pain, and those receiving ID-TIV are more likely to report redness, swelling, induration, and itching at the site than people receiving IM-TIV. Rhinitis, sore throat, and cough in the first 7 days following vaccination are the most common reactions to LAIV and occur significantly more often in participants receiving LAIV than in people receiving saline placebo. Severe adverse reactions following vaccination occur rarely, with one study putting the estimate at 0.9 per 100,000 ⁽⁶⁵⁾. A review of the Vaccine Adverse Events Reporting System (VAERS) in the USA estimated that annual rates of BGS ranged from 0.04 to 0.17 per 100,000 doses administered ⁽⁶⁸⁾.

APPENDIX A: EVIDENCE TABLE FOR INFLUENZA VACCINE EFFICACY & EFFECTIVENESS

Study	Vaccine	Study Design	Participants	Summary of Effectiveness Findings (95% CI)	Quality of Evidence
Trivalent Inactivated Influenza Vaccine (TIV) –lab-confirmed					
Ohmit SE, Victor JC, Rotthoff JR, et al. (2006). Prevention of antigenically drifted influenza by inactivated and live attenuated vaccines, <i>NEJM</i> , 355(24): 2513-2522.	Fluzone TIV, IM 15µg /strain; 0.5mL FluMist LAIV, IN 0.5mL Year: 2004- 2005 Mismatch of B strain	RCT, double blind, multi- centre	Age: 18-46 (mean 27) Sex: both (40% male) Healthy (excluded anyone for whom TIV is recommended in USA) Country: USA Setting: University & Community Sample size: PCR/culture IM: 519 IN: 522 Placebo: 206 Sample size: serology IM: 367 IN: 363 Placebo: 146	5-6 months, active follow-up RT-PCR &/or culture-positive (throat swab with ILI (1+ respiratory & 1+ systemic symptoms) <u>TIV vs placebo</u> TIV AR: 1.9% RR: 0.25 (0.10-0.58) VE: 75% (42-90) <u>TIV vs LAIV</u> RR: 0.47 (0.20-1.05) Relative reduction: 53% (-5-80) Placebo AR: 7.8% Serological infection (4-fold rise) <u>TIV vs placebo</u> RR: 0.22 (0.07-0.63) VE: 78% (37-93) <u>TIV vs LAIV</u> RR: 0.30 (0.10-0.77) Relative reduction: 70% (23-90) Culture or serologically positive <u>TIV vs placebo</u> RR: 0.33 (0.13-0.84) VE: 67% (16-87) <u>TIV vs LAIV</u>	Rank: I Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Effectiveness Findings (95% CI)	Quality of Evidence
				RR: 0.47 (0.20-1.04) Relative reduction: 53% (-4-80)	
Beran J, Wertzova V, Honegr K, et al. (2009). Challenge of conducting a placebo-controlled randomized efficacy study for influenza vaccine in a season with low attack rate and a mismatched vaccine B strain: a concrete example. <i>BMC Infectious Diseases</i> , 9:1-11	Fluarix TIV, IM 15µg/strain/0.5ml Placebo Saline Year 2005-2006 Mis-match, B strain	RCT, double blinded	Ages: 18-64 (mean age:39) Sex: both Healthy volunteers Country: Czech Republic Setting: not stated Sample Size: 6203 Vaccine: 4137 Placebo: 2066	240 day active (bi-weekly calls) follow-up Vaccine vs placebo Culture-confirmed (ILI with nasal & throat swabs): Any influenza AR: 0.6 vs 0.8% RR: 0.74 (0.43-1.40) VE: 22.3% (-49.1, 58.5) VE: influenza A: 25.1% (-260, 82) VE: influenza B: 21.5 (-66, 62) ILI (CDC-fever & cough or sore throat) AR: 6.0 vs 5.6 RR=1.06 (0.85, 1.32) VE: -6.1% (-33.8, 15.5)	Rank: I Quality: Good
Jackson LA, Gaglani MJ, Keyserling HL, et al. (2010). Safety, efficacy, and immunogenicity of an inactivated influenza vaccine in healthy adults: a randomized, placebo-controlled trial over two influenza seasons. <i>BMC Infectious</i>	Flulaval (Fluviral) TIV, IM 15µg/strain/0.5mL Placebo: saline Years 2005-2006 2006-	RCT double blind, multi-centre	Age: 18-49 (mean 32.7) Sex: both (40% male) Healthy Country: USA Setting: Health Center Sample size: 3714 vaccine 3768 placebo	5.5 month active (weekly calls) follow-up ILI definition: cough and 1+ respiratory or systemic symptoms Vaccine vs placebo (combined years) Culture-confirmed (ILI with culture-positive swab) AR: 0.8 vs 1.6 VE: 49.4% (20.3-69.7) Vaccine-matched, culture-confirmed	Rank: I Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Effectiveness Findings (95% CI)	Quality of Evidence
<i>Diseases</i> 10(71)	2007 Mismatch strain – B in 2006-07			AR: 0.6 vs 1.2 VE: 46.3% (9.8-56.1) Serological &/or culture-positive AR: 1.2 vs 3.2 VE: 63.2% (48.2-75.2)	
Ohmit SE, Victor JC, Teich ER, et al. (2008). Prevention of symptomatic seasonal influenza in 2005-2006 by inactivated and live attenuated vaccines, <i>Journal of Infectious Diseases</i> , 198(1):312-317.	Fluzone TIV, IM 15µg/strain; 0.5mL FluMist LAIV, IN 10 ^{6.5} -10 ^{7.5} MTCID /strain; 0.5mL Year: 2005-2006 Placebo: Saline	RCT double blind, multi-centre	Age: 18-48 (mean 25) Sex: both (40% male) Healthy (excluded anyone for whom TIVS is recommended in USA) Country: USA Setting: 4 university & 2 community sites *Participants who re-enrolled were assigned to same arm as previous year Sample size (PCR) IM: 867 IN: 853 Placebo: 338 **972/1247 re-enrolled from year 1 Sample size (serological)	RT-PCR &/or culture-positive (Throat swab with ILI (1+ respiratory & 1+ systemic symptoms) 180 days, active follow-up <u>TIV vs placebo</u> TIV AR: 1.5% RR: 0.84 (0.30-2.71) VE: 16% (-171-70) <u>TIV vs LAIV</u> RR: 0.91 (0.40-2.10) Relative reduction: 9% (-110-60) Serological infection (4-fold rise) 30 days post vaccine to end of season (~150 days) <u>TIV vs placebo</u> RR: 0.28 (0.11-0.67) VE: 72% (33-89) <u>TIV vs LAIV</u> RR: 0.78 (0.40-1.48) Relative reduction: 22% (-48-60) Culture &/or PCR &/or serologically positive	Rank: I Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Effectiveness Findings (95% CI)	Quality of Evidence
			IM: 867 IN: 853 Placebo: 338	<u>TIV vs placebo</u> RR: 0.46 (0.23-0.96) VE: 54% (4-77) <u>TIV vs LAIV</u> RR: 0.78 (0.40-1.48) Relative reduction: 22% (-48-60)	
Beran J, Vesikari T, Wertzova, et al. (2009). Efficacy of inactivated split-virus influenza vaccine against culture-confirmed influenza in healthy adults: A prospective, randomized, placebo-controlled trial. <i>Journal of Infectious Diseases</i> , 200:1861-1869	Fluarix TIV, IM 15ug/strain/ 0.5ml Placebo Saline Year 2006-2007	RCT, double blind, multi-centre	Ages: 18-64 (mean age 40) Sex: both (40% male) Healthy volunteers Country: Czech Republic and Finland Setting: not stated, self-referred participants Sample size TIV: 5103 Placebo: 2549	8 month active (bi-weekly calls) follow-up Vaccine vs placebo Culture-confirmed influenza (ILI with nasal & throat swabs) <u>Any influenza</u> AR: 1.2 (0.9-1.6) vs 3.2 (2.6-4.0) RR: 37.5 VE: 61.6 (46.0-72.8) <u>Antigenically-matched strains</u> AR: 0.96% (0.6-1.4) vs 2.9 (2.3-3.6) RR: 0.33 VE: 66.9% (51.9-77.4) ILI only (CDC definition) AR: 14.6 vs 18.0 RR: 0.81 VE: 17.9%	Rank: I Quality: Good
Vesikari T, Beran J, Durviaux S, et al. (2012). Use of real-time polymerase chain reaction (rtPCR) as a diagnostic tool	Fluarix TIV, IM, 15µg/strain/ 0.5mL	RCT, double blind	Age: Sex: Healthy Country: Czech Republic and	RT-PCR &/or culture-positive swabs Vaccine vs placebo AR: 2.1 (1.7-205) vs 4.7 (3.9-5.6) VE: 54.7 (40.7-65.4)	Rank: I Quality: Good NOTE:

Study	Vaccine	Study Design	Participants	Summary of Effectiveness Findings (95% CI)	Quality of Evidence
for influenza infection in a vaccine efficacy trial. <i>Journal of Clinical Virology</i> , 53:22-28.	Placebo: saline Year: 2006-2007		Finland Sample size: Vaccine: 5103 Placebo: 2549	ILI: 1+ systemic & 1+ respiratory symptoms Vaccine vs. placebo AR: 14.6 vs 18.0 VE: 19%	Same participants as in Beran et al, 2009
Baxter R, Patriarca PA, Ensor K, et al. (2011). Evaluation of the safety, reactogenicity and immunogenicity of FluBlok (R) trivalent recombinant baculovirus-expressed hemagglutinin influenza vaccine administered intramuscularly to healthy adults 50-64 years of age. <i>Vaccine</i> , 29:2272-2278.	Fluzone, TIV, IM 15µg/strain/0.5 mL Un-licensed recombinant TIV (not abstracted) Season 2007-2008	RCT, observer blinded	Age: 50-64 (mean 56) Sex: both (36% male) Healthy (acute & chronic illness not eligible) Country: USA Setting: Health centers Sample size TIV: 302	Culture-confirmed (immunofluorescence) NP swab 24-72h from symptom onset Vaccine vs comparator AR: 0.010 v 0.023 ILI: CDC def Passive follow-up AR: 0.0397 vs 0.0333 VE: -19%	Rank: I Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Effectiveness Findings (95% CI)	Quality of Evidence
Coleman BL, Boggild AK, Drews SJ, et al. (2011) Respiratory illnesses in Canadian health care workers: A pilot study of influenza vaccine and oseltamivir prophylaxis during the 2007/2008 influenza season. <i>Influenza and Other Respiratory Viruses</i> , 5: 405-408.	Fluviral TIV, IM 15µg/ 0.5ml Antiviral Pro-phylaxis: Osel-tamivir Year 2007-2008 Vaccine mismatch	RCT, Open label, lab techs blinded	Ages: 25-64 (mean 41) Sex: both Healthy Country: Canada Setting: Hospital Sample Size: Vaccinated: 14 Prophylaxis: 42	180 day active follow-up PCR-confirmed influenza (NP swab) Vaccinated vs prophylaxis AR: 16.7% (2.4-48) vs 24% (2.8-39), NS Relative VE: 30%	Rank: I Quality: Good
Frey S, Vesikari T, Szymczakiewicz-Multanowska A et al. (2010) Clinical efficacy of cell culture-derived and egg-derived inactivated subunit influenza vaccines in healthy adults. <i>Clinical Infectious Diseases</i> 51(9):997-1004	Agrippal TIV, IM, 0.5mL Year 2007-2008 Cell-culture-derived vaccine (not abstracted) Placebo: saline	RCT observer blind	Age: 18-49 (mean 33) Sex: both (44-45% male) Healthy Country: USA, Finland, Poland Setting: not stated Vaccine: 3676 Placebo: 3900	9 month, active (weekly calls) follow up Vaccine vs placebo PCR &/or culture confirmed (ILI with nasal & throat swabs) AR: 1.35 vs 3.64% VE : 63.0% (46.7-79.3) PCR &/or culture confirmed: Vaccine-like strains AR: 0.25 vs 1.1% VE: 78.4% (52.1-100) ILI (CDC definition) AR: 7 vs 9% VE: 22%	Rank: I Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Effectiveness Findings (95% CI)	Quality of Evidence
Monto AS, Ohmit SE, Petrie JG, et al. (2009). Comparative efficacy of inactivated and live attenuated influenza vaccines. <i>NEJM</i> , 361:1260-1267.	FluZone TIV, IM 15µg/0.5 mL FluMist LAIV, IN 10 ^{6.5-7.5} per 0.2mL Placebo Saline Year 2007-2008	RCT Double blind, placebo controlled	Ages: 18-49 (mean 23) Sex: both (38% male) Healthy (excluded anyone for whom TIV is recommended) Country: USA Setting: Community at 4 university sites, Michigan Sample Size: LAIV: 813 TIV: 814 Placebo: 325	6 month passive follow-up PCR &/or culture-positive (ILI: 2+ respiratory or systemic symptoms with throat swab) <u>TIV vs placebo</u> TIV AR: 3.4% RR: 0.32 (0.19-0.54) VE: 68% (46-81) <u>TIV vs LAIV</u> RR: 0.50 (0.31-0.80) Relative reduction: 50% (20-69)	Rank: I Quality: Good
Ohmit SE, Petrie JG, Cross RT, et al. (2011). Influenza hemagglutination-inhibition antibody titer as a correlate of vaccine-induced protection. <i>Journal of Infectious Diseases</i> , 204: 1879-1885.	Fluzone TIV, IM 15µg/0.5mL FluMist LAIV, IN Placebo: Saline Year: 2007-2008	RCT double blind, multi-centre	Age: 18-49 Sex: both Healthy (excluded anyone for whom TIV is recommended) Country: USA Setting: University & community Sample size TIV: 259 LAIV: 289 Placebo: 110	180 days, active follow-up RT-PCR for H3N2 only (Throat swab with ILI (1+ respiratory & 1+ systemic symptoms)) <u>TIV vs placebo</u> AR: 8.5 vs 27.3% RR: 0.25 (0.13-0.46) VE: 68.9% <u>TIV vs LAIV</u> AR: 18.3 vs 27.3% RR: 0.41 (0.24-0.70) Relative VE: 53.5%	Rank: I Quality: Good
Ito Y, Sumi H, Kato T. (2006)	TIV, IM,	Cohort, retro-	Age: 22-66 (mean	RAT positive: febrile episodes and positive rapid	Rank: II-2

Study	Vaccine	Study Design	Participants	Summary of Effectiveness Findings (95% CI)	Quality of Evidence
Evaluation of influenza vaccination in health-care workers, using rapid antigen detection test. <i>Journal of Infection & Chemotherapy</i> . 12: 70-72	0.5mL Year 2002-03	spective	36) Sex: both (28.3 vs 19.4% male) Country: Japan Setting: Hospital Sample size: 237 vaccinated 129 non-vaccinated	antigen detection test for influenza 120 day follow-up (questionnaire) vaccinated vs unvaccinated AR: 3.4 vs 8.5% RR= 0.4 (0.16-0.96) VE: 60%	Quality: Fair (selection /response bias large possible)
Influenza Like Illness (ILI) - RCT					
Duque, Moreno, Hurtado et al. (2001) Effectiveness of an anti-flu vaccine in a Colombian labor population. <i>Pan American Journal of Public Health/Revista Panamericana de Salud Publica</i> , 10:232-239.	Agrippal (Agriflu) TIV, IM 15µg/ 0.5mL Placebo: vitamin C Year 1996-1997	RCT, double blind	Age: 18-60 Sex: both (24.3% male) Healthy (excluded immune-suppressed) Country: Columbia Setting: Work sites Sample size: 247 vaccine 246 placebo	6 month active (bi-weekly) follow-up ILI (sore throat, cough, and fever of >24 hours) Vaccine vs placebo AR: 91.5 vs 78.5% RR: 0.86 (0.80-0.93) VE: 14% (7-20)	Rank: I Quality: Good
Kramer JS, Durham C, Schroeder T, Garrelts JC. (2006). Effectiveness of half-dose versus full-dose influenza vaccine in	Fluzone TIV, IM 15µg/ strain/ 0.5ml Comparator	Prospective, randomized, double blind trial	Ages: 18-65 Sex: both Health: employees but no eligibility restrictions stated Country: USA	5 month (active, monthly) follow-up for symptoms ILI (influenza diagnosis by private GP) Full- vs half-dose vaccine AR: 3.6 vs 6.8%	Rank: II Quality: Fair (passive follow-up, paucity of details on partici-

Study	Vaccine	Study Design	Participants	Summary of Effectiveness Findings (95% CI)	Quality of Evidence
health care workers. <i>Am J Health-Syst Pharm.</i> 63:2111-2115.	Half-dose (0.25mL) of Fluzone (not abstracted)		Setting: tertiary care hospital Sample size Full dose: 222 Half dose: 222	RR: 0.53 (0.43-1.64) Relative VE: 47% ILI (self-report of fever and cough) AR: 8.1 vs 9.4% RR: 0.83 (0.46-1.51) Relative VE: 17	pants)
	Year 2004-2005				

Influenza Like Illness (ILI) - Test-negative case-control studies

Skowronski, D.M., Masaro, C., Kwindt, T.L., et al. (2007). Estimating vaccine effectiveness against laboratory-confirmed influenza using a sentinel physician network: Results from the 2005-2006 season of dual A and B vaccine mismatch in Canada. <i>Vaccine</i> , 25:2842-51.	Fluviral TIV, 15µg/strain/0.5mL Year 2005-2006 Mismatch A/H3N2	Case-control, test negative	Age: 20-64 (abstracted) Sex: both (52% male) Health: no chronic condition Country: Canada Setting: sentinel physician offices Sample size Cases: 36 Controls, test neg: 165	Followed during influenza season Swab taken for ILI at physician consult PCR-confirmed infection Vaccinated: unvaccinated AR: 30.5% vs 39.4% VE: 23% PCR-confirmed Swab taken within 48 hours of onset AR: 38% vs 31% VE: 18%	Rank: II-2 Quality: Fair-Good (bias re: swabbing decision)
Fielding, J.E., Grant, K.A., Papadakis, G., et al. (2011).	Licensed Australian TIV, NOS	Case-control, test negative	Age: 20-64 (abstracted) Sex: both (52% male)	Swab taken for ILI at physician consult	Rank: II-2 Quality:

Study	Vaccine	Study Design	Participants	Summary of Effectiveness Findings (95% CI)	Quality of Evidence
Estimation of type- and subtype-specific influenza vaccine effectiveness in Victoria, Australia using a test negative case control method, 2007-2008. <i>BMC Infectious Diseases</i> , 11:170	Year 2007 & 2008 (southern hemisphere) Strain mismatch 2007		Health: all Country: Australia Setting: sentinel physician offices Sample size 2007: 289 2008: 238	PCR-confirmed VE (adjusted for month swab collected) 2007: 64% (29-82) 2008: 35% (-56-73)	Fair-Good (bias re: swabbing decision, health status unknown)
Eick-Cost, A.A., Tastad, K.J., Guerrero, A.C., et al. (2012). Effectiveness of seasonal influenza vaccines against influenza-associated illnesses among US military personnel in 2010-11: A case-control approach. <i>PLoS ONE</i> , 7:	TIV or LAIV, various licensed, USA NOS Year 2010-2011	Case-control, retrospective (test negative & healthy controls)	Age: 17-64 (~10% 40+ years old) Sex: both (70%+ male) Healthy military Country: USA Setting: Military Sample size Cases: 603 (288 TIV, 425 LAIV) Control, healthy: 1766 (302 TIV, 273 LAIV) Control, test neg: 2284 (1068 TIV, 1544 LAIV)	Swab collected for ILI at medical encounter PCR or culture-confirmed (NP or nasal wash) Vaccine effectiveness (adjusted*) <u>Test-negative controls (unmatched)</u> Any vaccine vs no vaccine 29% (-6-53) TIV vs no vaccine 53% (25-71) LAIV vs no vaccine 13% (-77-27) Healthy controls: medical encounter for non-respiratory illness Controls: test negative for ILI <u>Healthy controls** (non respiratory consult)</u> Any vaccine vs no vaccine 16% (-1-45) TIV vs no vaccine	Rank: II-2 Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Effectiveness Findings (95% CI)	Quality of Evidence
				23% (-1-42) LAIV vs no vaccine 11% (-15-31) *sex, age group, prior vaccinations ** sex, age, location	
Fielding JE, Grant KA, Tran T, et al. (2012). Moderate influenza vaccine effectiveness in Victoria, Australia, 2011. <i>Euro-surveillance</i> , 17(11):20115	Licensed Australia, NOS Year 2011, southern hemisphere	Case-control, test negative	Age: 20-64 (abstracted) Sex: both Health: all Country: Australia Setting: sentinel physician offices Sample size Cases: 85 Controls, test neg: 249	Swab taken for ILI at medical consults PCR-confirmed Adjusted* VE: 61% (-3-85) *month of swabbing and co-morbidities	Rank: II-2 Quality: Fair-Good (bias re: swabbing decision, includes all ages)

Influenza Like Illness (ILI) - Cohort studies

Millot JL, Aymard M, Bardol A. (2002). Reduced efficiency of influenza vaccine in prevention of influenza-like illness in working adults: a 7 month prospective survey in EDF Gaz de France employees, in	Un-specified, Licensed, France, NOS Year 1996-1997	Cohort, prospective	Age: 18-64 (mean 41) Sex: both (83% male) Health: all employees unless on long-term sick leave Country: France Setting: Employees of company	7 month passive follow up (clinician visit) Vaccinated vs unvaccinated ILI (fever with sudden onset of 1+ systemic and 1+ respiratory symptom) Vaccinated vs. unvaccinated AR: 7.0 (3.9-10.0) vs 9.6 (8.5-10.6) RR: 0.70 VE: 27.3% (13.8-53.5)	Rank: II-2 Quality: Good
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Study	Vaccine	Study Design	Participants	Summary of Effectiveness Findings (95% CI)	Quality of Evidence
Rhone-Alpes, 1996-1997. <i>Occupational Medicine</i> , 52: 281-292.			Sample size: 5785 Vaccinated: 301 Unvaccinated: 3662		
Jick H, Hagberg KW. (2010). Effectiveness of influenza vaccination in the United Kingdom, 1996-2007. <i>Pharmacotherapy</i> , 30:1199-1206.	Various licensed TIV, LAIV, UK, NOS Years 1996-97 - 2006-07	Cohort, retrospective using General Practice Research Data-base	Age: 20-49 & 50-69 Sex: both (~50%) Healthy Country: USA Setting: GP offices Sample size Cases: 2820 (20-49 yrs) 1423 (50-69 yrs) Controls: 11273 (20-49 yrs) 5695 (50-69 yrs)	Influenza or ILI diagnosis versus other diagnoses GP diagnosis of ILI or influenza 20-49 vs 50-69 years OR: 0.75 (0.45-1.5) vs 0.77 (0.58-1.03) VE: 25% vs 23% Controls: matched by age, sex, location, date of swab	Rank: II-3 Quality: Fair-Good (Administrative data)
Liu Y, Huang L, Wang J. (2004). Reduction of acute respiratory illness (ARI) due to a voluntary workplace influenza vaccination program: who are more likely to get the benefit? <i>J Occup Health</i> 46: 455-460	Vaxigrip TIV, IM, 0.5mL Years: 1998 & 1999	Cohort	Age: 18-64 (41) Sex: both (30.3% male) Healthy Country: Taiwan Setting: work sites Sample size: 925 vaccinated 1459 unvaccinated	4 month active follow-up ARI: sore throat with fever, cough, or any acute respiratory symptom AR: vaccinated vs unvaccinated 1998: 38.2 vs 19.1% 1999: 16.3 vs. 16.4 VE: 1998: -100% 1999: 0.3%	Rank: II-2 Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Effectiveness Findings (95% CI)	Quality of Evidence
Samad AH, Usul M, Zakaria D et al. (2004). Influenza vaccination in a Malaysian company: what are costs and benefits for the employer? <i>International Congress Series</i> 1263: 585-589	Vaxigrip, TIV, IM, 0.5mL Years 2000-01 Comparator: no vaccine	Cohort	Age: 18-64 Sex: Both (77.6% male) Country: Malaysia Setting: Work sites Sample size: 504 vaccine 518 no vaccine	ILI: fever 3-5 days and 2+ of chills, headache, runny nose, sore throat, cough, muscle aches, tiredness and weakness 6 month active follow up AR: 8.13 vaccinated 30.3 non vaccinated VE: 73.16%	Rank: II-2 Quality: Good
Samad, A.H., Usul, M., Zakaria, D., et al. (2006). Workplace vaccination against influenza in Malaysia: Does the employer benefit? <i>Journal of Occupational Health</i> , 48: 1-10.	Vaxigrip TIV, IM 15µg/strain/ 0.5mL Year 2000-2001	Cohort, prospective	Age: 18-64 (mean 32-33) Sex: both (80% male) Healthy employees, excluded chronic diseases Country: Malaysia Setting: Company Sample size: 1022 504 vaccinated 518 not vaccinated	ILI: at least 2 days duration, with at least one systemic symptom (fever, chills, myalgia), and at least one respiratory tract symptom (rhinorrhoea, sore throat, cough, hoarseness) 180 day active follow up (bimonthly report) AR: 0.0813 vs 0.303 VE: 73.16%	Rank: II-2 Quality: Good
Nichol, KL, D'Heilly S, & Ehlinger EP, (2008). Influenza vaccination among college and university students:	TIV or LAIV, various licensed, USA NOS	Cohort, prospective	Age: 18+ (mean 23-25) Sex: both (25-29% male) Healthy full-time university students	6 month active (monthly email) follow-up ILI (acute respiratory illness with fever/feverishness and cough)	Rank: II-2 Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Effectiveness Findings (95% CI)	Quality of Evidence
Impact on influenza-like illness, health care use, and impaired school performance. <i>Archives of Pediatrics & Adolescent Medicine</i> , 162, 1113-1118.	Years: 2002-03-2005-06 Mismatch strain in 2003-04		Country: USA Setting: Universities Sample Size: Vaccinated: 3864 Unvaccinated: 8932	Vaccinated vs unvaccinated AR: 20.9 vs 25.5% OR 0.77 VE: 18%	
Wang Z, Tobler S, Roayaei J, Eick A. (2009). Live attenuated or inactivated influenza vaccines and medical encounters for respiratory illnesses among US military personnel. <i>JAMA</i> 301(9): 945-953	Licensed TIV & LAIV, NOS Years: 2004-05 2005-06 2006-07 Comparator: no vaccine	Cohort	Age: 19-49 Sex: Both (~80% male) Country: USA Setting: US military Sample size: 2004-05 TIV: 366,201 LAIV: 184,707 None: 510,820 2005-06 TIV: 626,478 LAIV: 143,054 None: 271,732 2006-07 TIV: 436,600 LAIV: 400,630 None: 230,729	ILI: health care encounter with primary diagnosis code of pneumonia or influenza 36 months active follow-up AR: TIV vs LAIV vs placebo 2004-05: 0.26 vs 0.44 vs 0.53 2005-06: 0.29 vs 0.44 vs 0.42 2006-07: 0.28 vs 0.48 vs 0.47 VE TIV vs no vaccine 2004-05: 54.8% (51.3-58.1) 2005-06: 30.7% (24.7-36.2) 2006-07: 28.4% (21.9-34.3) LAIV vs no vaccine 2004-05: 20.8% (12.3-28.5) 2005-06: 12.0% (1.7-21.3) 2006-07: 10.7% (2.7-18.1) TIV vs LAIV 2004-05: 43.0% (36.4-48.9) 2005-06: 21.2% (13.5-28.2) 2006-07: 19.8% (13.6-25.5)	Rank: II Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Effectiveness Findings (95% CI)	Quality of Evidence
At'kov, O.Y., Azarov, A.V., Zhukov, D.A., et al. (2011). Influenza vaccination in healthy working adults in Russia: observational study of effectiveness and return on investment for the employer, <i>Applied health economics and health policy</i> , 9: 89-99.	Vaxigrip TIV, IM 15µg/strain/0.5mL Year: 2005-2006	Cohort, prospective	Age: 18-64 (mean 39) Sex: both (55% male) Healthy employees Country: Russia Setting: transport company Sample size Vaccinated: 701 Unvaccinated: 630	Active follow-up (monthly GP visit, questionnaires) ILI: fever (≥ 2 days), at least 1 of (fever, rigors, or myalgia), and 1 respiratory symptom (coryza, sore throat, cough, or hoarseness) TIV vs unvaccinated AR: 6.8 vs 23.2% VE: 70%	Rank: II-2 Quality: Good
Nichol KL, D'Heilly SJ, Greenberg ME, Ehlinger E. (2009) Burden of Influenza-Like Illness and Effectiveness of Influenza Vaccination among Working Adults aged 50-64 years. <i>Clinical Infectious Diseases</i> 48: 292-298	2006-07 vaccine, NOS	Cohort, prospective	Age: 50-64 Sex: both (22.5% male) Health: All Country: USA Setting: University Sample size: 404 vaccinated 93 not vaccinated	Follow-up: influenza season ILI: definition: fever with cough or sore throat Vaccinated vs unvaccinated AR: 15.7 vs 25.0% OR: 0.55 VE: 0.48 (0.27-0.86)	Rank: II-2 Quality: Good
Phillips CJ, Woolpert T, Seveck C, et al. (2013). Comparison of the Effectiveness of	LAIV, dose not stated Years 2006-	Cohort	Age: 18-49 (median 27) Sex: both (72.4% male) Healthy	200 days passive follow up: physician consult and ICD-9 codes of visit AR: TIV vs LAIV ILI (ICD-9 codes):	Rank: II-2 Quality: Fair-Good

Study	Vaccine	Study Design	Participants	Summary of Effectiveness Findings (95% CI)	Quality of Evidence
trivalent inactivated influenza vaccine and live, attenuated influenza vaccine in preventing influenza-like illness among US military service members, 2006–2009. <i>Clinical Infectious Diseases</i> 56(1): 11-19.	2009 Comparator: TIV		Country: USA Setting: US military Sample Size: LAIV: 9489 TIV: 32181	14.0 vs 14.2% Influenza (ICD-9): 0.46 vs 0.38% Pneumonia &/or influenza: 0.76 vs 0.73% Relative VE (influenza): 17%	

Live Attenuated Influenza Virus Vaccine (LAIV) –lab-confirmed

Ohmit SE, Victor JC, Rotthoff JR, et al. (2006). Prevention of antigenically drifted influenza by inactivated and live attenuated vaccines, <i>NEJM</i> , 355(24): 2513-2522.	Fluzone TIV, IM 15µg/strain; 0.5mL FluMist LAIV, IN 0.5mL Year: 2004-2005 Mismatch of B strain	RCT, double blind, multi-centre	Age: 18-46 (mean 27) Sex: both (40% male) Healthy (excluded anyone for whom TIV is recommended in USA) Country: USA Setting: University & Community Sample size: PCR/culture IM: 519 IN: 522 Placebo: 206	5-6 months, active follow-up RT-PCR &/or culture-positive (throat swab with ILI (1+ respiratory & 1+ systemic symptoms) <u>LAIV vs placebo</u> LAIV AR: 4.0% RR: 0.52 (0.26-1.07) VE: 48% (-7-74) <u>TIV vs LAIV</u> RR: 0.47 (0.20-1.05) Relative reduction: 53% (-5-80) Placebo AR: 7.8% Serological infection (4-fold rise)	Rank: I Quality: Good
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Study	Vaccine	Study Design	Participants	Summary of Effectiveness Findings (95% CI)	Quality of Evidence
			Sample size: serology IM: 367 IN: 363 Placebo: 146	<u>LAIV vs placebo</u> RR: 0.72 (0.33-1.67) VE: 28% (-67-67) <u>TIV vs LAIV</u> RR: 0.30 (0.10-0.77) Relative reduction: 70% (23-90) Culture <u>or</u> serologically positive <u>LAIV vs placebo</u> RR: 0.70 (0.33-1.57) VE: 30 (-57-67) <u>TIV vs LAIV</u> RR: 0.47 (0.20-1.04) Relative reduction: 53% (-4, 80)	
Ohmit SE, Victor JC, Teich ER, et al. (2008). Prevention of symptomatic seasonal influenza in 2005-2006 by inactivated and live attenuated vaccines, <i>Journal of Infectious Diseases</i> , 198(1):312-317.	Fluzone TIV, IM 15µg/strain; 0.5mL FluMist LAIV, IN 10 ^{6.5} -10 ^{7.5} MTCID /strain; 0.5mL Year: 2005-2006	RCT double blind, multi-centre	Age: 18-48 (mean 25) Sex: both (40% male) Healthy (excluded anyone for whom TIVS is recommended in USA) Country: USA Setting: 4 university & 2 community sites *Participants who re-enrolled were assigned to same	180 days, active follow-up RT-PCR &/or culture-positive (Throat swab with ILI (1+ respiratory & 1+ systemic symptoms)) <u>LAIV vs placebo</u> LAIV AR: 1.6% RR: 0.92 (0.33-2.94) VE: 8 (-194 to 67) <u>TIV vs LAIV</u> RR: 0.91 (0.40-2.10) Relative reduction: 9% (-110-60) Serological infection (4-fold	Rank: I Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Effectiveness Findings (95% CI)	Quality of Evidence
	Placebo: Saline		arm as previous year Sample size (PCR) IM: 867 IN: 853 Placebo: 338 **972/1247 re-enrolled from year 1 Sample size (serological) IM: 867 IN: 853 Placebo: 338	rise) 30 days post vaccine to end of season (~150 days) <u>LAIV vs placebo</u> RR: 0.65 (0.32-1.37) VE: 35% (-37-68) <u>TIV vs LAIV</u> RR: 0.78 (0.40-1.48) Relative reduction: 22% (-48-60) Culture &/or PCR &/or serologically positive <u>LAIV vs placebo</u> RR: 0.60 (0.30-1.20) VE: 40% (-20-70) <u>TIV vs LAIV</u> RR: 0.78 (0.40-1.48) Relative reduction: 22% (-48-60)	
Monto AS, Ohmit SE, Petrie JG, et al. (2009). Comparative efficacy of inactivated and live attenuated influenza vaccines. <i>NEJM</i>, 361:1260-1267.	Fluzone TIV, IM 15µg/ 0.5mL FluMist LAIV, IN 10^{6.5-7.5} per 0.2mL Placebo Saline	RCT Double blind, placebo controlled	Ages: 18-49 (mean 23) Sex: both (38% male) Healthy (excluded anyone for whom TIV is recommended) Country: USA Setting: Community at 4 university sites, Michigan Sample Size:	6 month passive follow-up PCR &/or culture-positive (ILI: 2+ respiratory or systemic symptoms with throat swab) <u>LAIV vs placebo</u> LAIV AR: 6.9% RR: 0.64 (0.41-1.00) VE: 36% (0-59) <u>TIV vs LAIV</u> RR: 0.50 (0.31-0.80)	Rank: I Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Effectiveness Findings (95% CI)	Quality of Evidence
	Year 2007-2008		LAIV: 813 TIV: 814 Placebo: 325	Relative reduction: 50% (20-69)	
Block, S.L., Yorgev, R., Hayden, F.G., et al. (2008). Shedding and immunogenicity of live attenuated influenza vaccine virus in subjects 5-49 years of age. <i>Vaccine</i> , 26: 4940-4946.	FluMist 10 ⁷ TCID/ 0.5mL Year: 2004-2005	Cohort, open-label, single arm, multi-center, phase IV	Age: 18-49 (mean 30) Sex: both (37.4% male) Healthy volunteers Country: USA Setting: Health center Sample size: 115	RT-PCR for Influenza 28 day active follow-up AR: 17%	Rank: II-2 Quality: Good

Live Attenuated Influenza Virus Vaccines (LAIV) – Influenza Like Illness (ILI)

Eick-Cost, A.A., Tastad, K.J., Guerrero, A.C., et al. (2012). Effectiveness of seasonal influenza vaccines against influenza-associated illnesses among US military personnel in 2010-11: A case-control approach. <i>PLoS ONE</i> , 7:	TIV or LAIV, various licensed, USA NOS Year 2010-2011	Case-control, retrospective (test negative & healthy controls)	Age: 17-64 (~10% 40+ years old) Sex: both (70%+ male) Healthy military Country: USA Setting: Military Sample size Cases: 603 (288 TIV, 425 LAIV) Control, healthy: 1766 (302 TIV, 273 LAIV) Control, test neg: 2284 (1068 TIV,	Passive, swab collected for ILI at medical encounter PCR or culture-confirmed (NP or nasal wash) Vaccine effectiveness: <u>Test-negative controls (unmatched*)</u> Any vaccine vs no vaccine 29% (-6-53) TIV vs no vaccine 53% (25-71) LAIV vs no vaccine 13% (-77-27) <u>Healthy controls (matched**, encounter for non-respiratory illness)</u>	Rank: II-2 Quality: Good
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Study	Vaccine	Study Design	Participants	Summary of Effectiveness Findings (95% CI)	Quality of Evidence
			1544 LAIV)	Any vaccine vs no vaccine 16% (-1-45) TIV vs no vaccine 23% (-1-42) LAIV vs no vaccine 11% (-15-31) *sex, age group, number of prior vaccinations ** sex, age, location	
Jick H, Hagberg KW. (2010). Effectiveness of influenza vaccination in the United Kingdom, 1996-2007. <i>Pharmacotherapy</i> , 30:1199-1206.	Various licensed TIV, LAIV, UK, NOS Years 1996-97 - 2006-07	Cohort, retrospective using GPRD (General Practice Research Database)	Age: 20-49 & 50-69 Sex: both (~50%) Healthy Country: USA Setting: GP offices Sample size Cases: 20-49: 2820 50-69: 1423 Controls: 20-49: 11273 50-69: 5695	Influenza or ILI diagnosis versus other diagnoses GP diagnosis of ILI or influenza 20-49 vs 50-69 years OR: 0.75 (0.45-1.5) vs 0.77 (0.58-1.03) VE: 25% vs 23% Controls matched by age, sex, location, date	Rank: II-3 Quality: Fair-Good (Administrative data)
Nichol, KL, D'Heilly, S, & Ehlinger, EP, (2008) Influenza vaccination among college and university students: Impact on influenza-like illness, health care use, and	TIV or LAIV, various licensed, USA NOS Years: 2002-03-2005-06	Cohort, prospective	Age: 18+ (mean 23-25) Sex: both (25-29% male) Healthy full-time university students Country: USA Setting: Universities	6 month active (monthly email) follow-up Vaccinated vs unvaccinated ILI (acute respiratory illness with fever/feverishness and cough) AR: 20.9 vs 25.5% OR 0.77 VE: 18%	Rank: II-2 Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Effectiveness Findings (95% CI)	Quality of Evidence
impaired school performance. <i>Archives of Pediatrics & Adolescent Medicine</i> , 162, 1113-1118.	Mismatch strain in 2003-04		Sample Size: Vaccinated: 3864 Unvaccinated: 8932		
Phillips CJ, Woolpert T, Sevick C, et al. (2013). Comparison of the Effectiveness of trivalent inactivated influenza vaccine and live, attenuated influenza vaccine in preventing influenza-like illness among US military service members, 2006–2009. <i>Clinical Infectious Diseases</i> 56(1): 11-9.	LAIV, dose not stated Years 2006-2009 Comparator: TIV	Cohort	Age: 18-49 (median 27) Sex: both (72.4% male) Healthy Country: USA Setting: US military Sample Size: LAIV: 9489 TIV: 32181	200 days passive follow up: physician consult and ICD-9 codes of visit AR: TIV vs LAIV ILI (ICD-9 codes): 14.0 vs 14.2% Influenza (ICD-9): 0.46 vs 0.38% Pneumonia &/or influenza: 0.76 vs 0.73% Relative VE (influenza): 17%	Rank: II-2 Quality: Fair-Good
Wang Z, Tobler S, Roayaei J, Eick A. (2009). Live attenuated or inactivated influenza vaccines and medical encounters for respiratory illnesses among	Licensed TIV & LAIV, NOS Years: 2004-05 2005-06 2006-07	Cohort	Age: 19-49 Sex: Both (~80% male) Country: USA Setting: US military Sample size:	36 months active follow-up ILI: health care encounter with primary diagnosis code of pneumonia or influenza AR: LAIV vs placebo 2004-05: 0.26 vs 0.44 vs 0.53	Rank: II Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Effectiveness Findings (95% CI)	Quality of Evidence
US military personnel. <i>JAMA</i> 301(9): 945-953	Comparator: no vaccine		2004-05 TIV: 366,201 LAIV: 184,707 None: 510,820 2005-06 TIV: 626,478 LAIV: 143,054 None: 271,732 2006-07 TIV: 436,600 LAIV: 400,630 None: 230,729	2005-06: 0.29 vs 0.44 vs 0.42 2006-07: 0.28 vs 0.48 vs 0.47 VE: TIV vs no vaccine 2004-05: 54.8% (51.3-58.1) 2005-06: 30.7% (24.7-36.2) 2006-07: 28.4% (21.9-34.3) LAIV vs no vaccine 2004-05: 20.8% (12.3-28.5) 2005-06: 12.0% (1.7-21.3) 2006-07: 10.7% (2.7-18.1) TIV vs LAIV 2004-05: 43.0% (36.4-48.9) 2005-06: 21.2% (13.5-28.2) 2006-07: 19.8% (13.6-25.5)	

Various Vaccines – Lab confirmed

Kissling E, Valenciano M, Cohen JM et al. (2011). I-MOVE multi-centre case control study 2010-11: Overall and stratified estimates of influenza vaccine effectiveness in Europe. <i>PloS ONE</i> 6(11): e27622	Various TIV, IM Year: 2010-2011	Case-control, multi-center	Age: All (median for cases 23, controls 32) Sex: Both (47.9% male) Country: France, Hungary, Ireland, Italy, Poland, Portugal, Romania, Spain Sample size: Vaccine: 337 No vaccine: 4073	RT-PCR or culture (NP swab) Swab within 8 days of ILI onset Vaccinated vs not vaccinated AR: 24% vs 52% OR: 0.29 (all ages) VE: 15-59 years Crude: 56.5% (31.2, 72.6) Adjusted*: 41.3% (-2.6, 66.4)	Rank: II-2 Quality: Good
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*Adjusted for 2009-10 seasonal and pandemic influenza vaccination, chronic disease, sex, recent hospitalisation for chronic disease, smoking, age group,

Study	Vaccine	Study Design	Participants	Summary of Effectiveness Findings (95% CI)	Quality of Evidence
				practitioner visits in previous year, week of symptom onset	

AR: attack rate

ARI: acute respiratory illness

CHMP: European Committee for Medical Products for Human Use

GBS: Guillain Barré Syndrome

GMT: geometric mean titer

GMTR: geometric mean titer ratio

GP: general practitioner

ILI: influenza-like illness

IM: intramuscular

ID: intradermal

IN: intranasal

LAIV: live attenuated influenza virus

NOS: not otherwise specified

OR: odds ratio

PCR: polymerase chain reaction

RCT: randomized controlled trial

RR: relative risk

TIV: trivalent inactivated (influenza) vaccine

VE: vaccine effectiveness

vs: versus

APPENDIX B: EVIDENCE TABLE FOR INFLUENZA VACCINE IMMUNOGENICITY

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95% CI)	Quality of Evidence
Trivalent Inactive Influenza Vaccines (TIV)					
Frey S, Poland G, Percell S, Podda A. (2003). Comparison of the safety, tolerability, and immunogenicity of a MF59-adjuvanted influenza vaccine and a non-adjuvanted influenza vaccine in non-elderly adults. <i>Vaccine</i> 21:4234-4237	Fluzone TIV, IM 15µg/strain/ 0.5mL Comparator: Fluad (not abstracted) Years 1995-96 and 1996-97	RCT, randomized, observer blind	Age: 18-65 Sex: both Country: USA Healthy Sample size: 1995-96: 151 1996-97: 96 Comparator: 150 (S1) 104(S2)	28 day follow-up 1995-96 vs 1996-97 Seroconversion (CHMP) H1N1: 53 vs 23% H3N2: 75 vs 32% B: 71 vs 28% Seroprotection (≥1:40) H1N1 95 vs 86% H3N2 91 vs 26% B 97 vs 69% GMT H1N1 850; 263 H3N2 418; 71 B 601; 176	Rank: I Quality: Good
Belshe RB, Newman FK, Cannon J. (2004). Serum antibody responses after intradermal vaccination against influenza. <i>New England Journal of Medicine</i> , 351:2286-2294.	Fluzone TIV, IM 15µg/strain/ 0.5mL Comparator: Un-licensed TIV, ID 0.6µg/strain/ 0.1mL (not ab-	RCT, open label	Age: 18-60 (mean 39) Sex: both (37% male) Healthy Country: USA Setting: Health Centers Sample size: Fluzone 69 Comparator 61	Follow-up: 21 days Seroconversion (CHMP): H1N1: 42.9 (30.5-56.0) H3N2: 33.3 (22.0-46.3) B 42.9 (30.5-56.0) Seroprotection (CHMP; 1:40+) H1N1: 100% H3N2: 100% B: 100% GMTR & GMT H1N1: 3.9 (2.9-5.3), 361 (280-467)	Rank: I Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95% CI)	Quality of Evidence
	stracted) Year 2001-2002		Total 130	H3N2: 3.6 (2.6-5.1), 271 (214-344) B: 3.6 (2.7-4.8), 508 (413-625)	
Chen, WH, Cross, AS, Edelman, R, et al. (2011). Antibody and Th1-type cell-mediated immune responses in elderly and young adults immunized with the standard or a high dose influenza vaccine. <i>Vaccine</i> , 29:2865-2873	Fluzone TIV, IM 15µg/strain/0.5mL Comparison Older adults (not abstracted) Year 2004-05	Controlled Trial	Age: 20-40 (mean 28) Sex: both (64% male) Healthy Country: USA Setting: Health Centres Sample size: 14	Follow-up: 28 days Seroconversion (4-fold rise) H1N1: 64% H3N2: 43% B: 79% Seroprotection (HAI titres ≥1:32): H1N1: 100% H3N2: 100% B: 79% IgA seroconversion (4-fold rise) H1N1: 50% H3N2: 14% B: 14%	Rank: II-1 Quality: Fair-Good (small sample size)
Engler, RJM, Nelson, MR, Klote, MM et al. (2008). Half- vs Full-Dose Trivalent Inactivated Influenza Vaccine (2004-2005) Age, Dose, and Sex Effects on Immune Responses. <i>Arch Intern Med</i> . 168(22): 2405-	Fluzone TIV, IM 15µg/strain/0.5mL Comparator: Half dose (not abstracted)	RCT Single blinded	Age: 18-64 (stratified by 18-49 and 50-64) Sex: both 56% male Healthy Country: UK Setting: Health Centers Sample Size: 554	21 day follow-up 18-49 years vs 50-64 years Seroconversion (4-fold increase) H1N1: 16.4 vs 15.7% H3N2: 38% v 37.1% B: 40.5% v 41.8% Seroprotection (≥1:40) H1N1: 54% v 38.9% H3N2: 75.5 v 72.5% B: 82.5% v 70.7% GMT	Rank: I Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95% CI)	Quality of Evidence
2414	Year 2004-05		18-49: 274 50-64: 280	H1N1: 28.8 (25.2-32.8) v 21.4 (18.6-24.7) H3N2: 55.2 (48.7-62.5) v 59 (51.4-67.8) B: 69.6 (61.4-78.9) v 52.1 (45.5-59.8)	
Treanor JJ, Campbell JD, Brady RC, et al. (2005). Rapid licensure of a new, inactivated influenza vaccine in the United States. <i>Human Vaccines</i> , 1:239-244	Fluarix TIV, IM 15µg/ strain/ 0.5mL Placebo: Saline Year 2004- 2005	RCT, double blind	Age: 18-64 (mean 39) Sex: both Healthy volunteers Country: USA Setting: not stated Sample size Vaccinated: 535 (18-49) 210 (50-64) Placebo: 190	Day 21 blood sample 18-49 years vs 50-64 years Seroconversion (4-fold rise) H1N1 67 (62-71) vs 42 (35- 49) H3N2 66 (1-70) vs 52 (45-59) B 82 (78-85) vs 67 (60- 7) GMTR H1N1 14.4 vs 4.2 H3N2 8.0 vs 4.6 B 11.8 vs 7.6 Seroprotection (CHMP: 18- 64 years) H1N1 97 (95-98) H3N2 99 (98-100) B 99 (98-100) For all participants: Seroconversion (4-fold increase) H1N1: 60% (56-63) H3N2: 62% (58-65) B: 78% (74-81) Seroprotection (≥1:40) H1N1 : 98%	Rank: I Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95% CI)	Quality of Evidence
				H3N2 : 99% B : 99% GMT H1N1 : 438.3(393.1-488.6) H3N2: 425 (393.1-459.5) B: 337.7(313-363.2)	
Beran J, Wertzova V, Honegr K, et al. (2009). Challenge of conducting a placebo-controlled randomized efficacy study for influenza vaccine in a season with low attack rate and a mismatched vaccine B strain: a concrete example. <i>BMC Infectious Diseases</i> , 9:1-11	Fluarix TIV, IM 15µg/strain/ 0.5ml Placebo Saline Year 2005-2006 Mis-match strain	RCT, double blinded	Ages: 18-64 (mean age:39) Sex: both Healthy volunteers Country: Czech Republic Setting: not stated Sample Size Vaccine: 632	Follow-up: 21 days Seroconversion (CHMP) H1N1: 89.2% (86.6-91.5%) H3N2: 77.2% (73.7-80.4%) B: 82.9% (79.7-85.8%) Seroprotection (HAI >=1:40) H1N1: 97.8% (96.31-98.78%) H3N2: 88.1% (85.35-90.55%) B: 95.9% (94.03-97.30%) GMT: H1N1: 730.5 (648.1-823.3) H3N2: 131.7 (119.9-144.6) B: 191.1 (175.7-207.9)	Rank I Quality: Good
Durando P, Fenoglio D, Boschini A, et al. (2008). Safety and immuno-genicity of two influenza virus subunit vaccines, with or without MF59adjuvant, administered to human immunodeficient	Agrippal TIV, IM 15µg/strain/ 0.5mL Comparison Fluad, adjuvanted	RCT No blinding	Age: 18-65 (mean 32) Sex: both (89% male) Healthy (seronegative for HIV-1) Country: Italy Setting: Health Center	Follow-up: 30 days Seroconversion (CHMP) H1N1 59% H3N2 69% B 63% Seroprotection (CHMP) 30 vs 90 days post-vaccination H1N1 : 90 vs 91%	Rank: I Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95% CI)	Quality of Evidence
cy virus Type 1-seropositive and -seronegative adults. <i>Clin. Vaccine Immunol.</i> 15(2): 253-259	(not abstracted) Year 2005-2006		Sample size: TIV: 80	H3N2 : 97 vs 98% B: 93 vs 94% GMTR D30/D0 vs D90/D0 H1N1 7.4 vs 5.6 H3N2 7.6 vs 4.7 B 6.8 vs 5.1	
Jackson LA, Gaglani MJ, Keyserling HL, et al. (2010). Safety, efficacy, and immunogenicity of an inactivated influenza vaccine in healthy adults: A randomized, placebo-controlled trial over two influenza seasons. <i>BMC Infectious Diseases</i> 10(71).	Flulaval TIV. IM 15µg/strain/ 0.5mL Placebo: saline Years 2005-2006 2006-2007	RCT Randomized, double blind (administering nurse not blinded)	Age: 18-49 (mean 32.7) Sex: Both (40% male) Healthy Setting: Health Center Country: USA Sample size Vaccine: 3714 Placebo: 3798	Follow-up: 21 days Seroconversion (CHMP) 2005-06 vs 2006-07 H1N1: 68 (65-71) vs 68 (63-72) H3N2: 85 (82-87) vs 72 (67-76) B: 82 (79-84) vs 74 (70-78) Seroprotection (≥1:40) H1N1: 97 (96, 98) vs 98 (97, 99) H3N2: 94 (92, 96) vs 92 (90, 95) B: 98 (97, 99) vs 97 (96, 99) GMFR H1N1: 11.0 (10.0-12.0) vs 9.9 (8.5-11.5) H3N2: 15.8 (14.6-17.2) vs 10.6 (9.3-12.1) B: 12.4 (11.3-13.5) vs 11.4 (10-13.1)	Rank: I Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95% CI)	Quality of Evidence
Zhu, F.C., Zhou, W.Z., Pan, H.X., et al. (2008). Safety and immunogenicity of two subunit influenza vaccines in healthy children, adults and the elderly: A randomized controlled trial in China. <i>Vaccine</i> , 26:4579-84.	Agrippal TIV, IM 15µg/strain/ 0.5mL Season 2005-2006 Comparator: Influvac (not abstracted)	RCT, unblinded except lab staff	Age: 18-59 (median 38) Sex: both (49.5% male) Healthy volunteers (no immune suppressing drugs, no pregnant women) Country: China Setting: Health center Sample size TIV: 99	Day 28 blood samples Seroconversion (4-fold rise) H1N1 72 (62-81) H3N2 77 (67-85) B 81 (71-89) Seroprotection (HA1 ≥1:40) H1N1 99 (94-100) H3N2 87 (78-93) B 94 (88-98) GMTR H1N1 5.5 H3N2 13.2 B 10.2	Rank: I Quality: Good
Belshe RB, Newman FK, Wilkins K, et al. (2007). Comparative immunogenicity of trivalent influenza vaccine administered by intradermal or intramuscular route in healthy adults. <i>Vaccine</i> , 25:6755-6763.	Fluzone, IM TIV 15µg/strain/ 0.5mL Season 2006-2007	RCT, open label	Age: 18-50 (mean 28-32) Sex: both (19% male) Healthy (immunosuppressed or pregnant not eligible) Country: USA Setting: Health centers Sample size TIV: 31	28 day follow-up Seroconversion (4-fold rise) H1N1 77.4% (58.9, 90.4) H3N2 100% (88.8, 100) B 90.3% (74.2, 98.0) Seroprotection (≥1:32) H1N1 67.7% (48.6, 83.3) H3N2 93.5% (78.6, 99.2) B 67.7% (48.6, 83.3) GMTR H1N1 10.2 H3N2 17.9 B 7.5	Rank: I Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95% CI)	Quality of Evidence
Beran J, Vesikari T, Wertzova, et al. (2009). Efficacy of inactivated split-virus influenza vaccine against culture-confirmed influenza in healthy adults: A prospective, randomized, placebo-controlled trial. <i>Journal of Infectious Diseases</i> , 2009:1861-1869.	Fluarix TIV, IM 15µg/ strain/ 0.5ml Placebo Saline Year 2006- 2007	RCT, double blind, multi-centre	Ages: 18-64 (mean 40) Sex: both (40% male) Healthy Country: Czech Republic and Finland Setting: not stated Sample size TIV: 5103 Placebo: 2549	Follow-up: 21-28 days Seroconversion (CHMP): H1N1: 76.3 (71.0-81.1) H3N2: 73.9 (68.4-78.8) B: 85.2 (80.6-89.1) Sero-protection (CHMP) H1N1: 97.6 (95.1-99.0) H3N2: 86.9 (82.5-90.6) B: 96.2 (93.3-98.1) GMTR H1N1: 20.0 (16.2-24.7) H3N2: 12.6 (10.7-14.9) B: 16.0 (13.7-18.6)	Rank: I Quality: Good
Luytjes W, Enouf V, Schipper M, et al. (2012). HI responses induced by seasonal influenza vaccination are associated with clinical protection and with seroprotection against non-homologous strains. <i>Vaccine</i> , 30:5262-69.	Vaxigrip 15µg/ 0.5mL TIV, IM Year 2006- 2007	Cohort	Age: 20-59 (mean 45) Sex: both (55% male) Healthy employees Country: Netherlands Setting: Company Sample size: 189	Day 28 blood samples Seroconversion (4-fold rise) H1N1 24% H3N2 42% B 32% Seroprotection (≥1:40 titres) H1N1 86.3 H3N2 83 B 55.5 GMTR H1N1 2.3 H3N2 3.2 B 2.6	Rank: II-2 Quality: Good
Baxter R, Patriarca PA, Ensor K, et al. (2011).	Fluzone, TIV, IM 15µg/	RCT, observer blinded	Age: 50-64 (mean 56) Sex: both (36%)	28 day follow-up	Rank: I

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95% CI)	Quality of Evidence
Evaluation of the safety, reactogenicity and immunogenicity of FluBlok (R) trivalent recombinant baculovirus-expressed hemagglutinin influenza vaccine administered intramuscularly to healthy adults 50-64 years of age. <i>Vaccine</i> , 29:2272-2278.	strain/ 0.5mL Un-licensed recombinant TIV (not abstracted) Season 2007-2008		male) Healthy (acute & chronic illness not eligible) Country: USA Setting: Health centers Sample size TIV: 302	Seroconversion (CHMP) H1N1 66% (60.6, 71.5) H3N2 44% (38.0, 49.5) B 41% (35.5, 46.8) Seroprotection ($\geq 1:40$) H1N1 96% (92.8-97.7) H3N2 75% (69.9-79.9) B 94% (91.1-96.7) GMTR H1N1 5.0 H3N2 3.3 B 2.4	Quality: Good
Frey S, Vesikari T, Szymczakiewicz-Multanowska A et al. (2010) Clinical Efficacy of Cell Culture-Derived and Egg-Derived Inactivated Subunit Influenza Vaccines in Healthy Adults. <i>Clinical Infectious Diseases</i> 51(9):997-1004	Agrippal (Agriflu) TIV, IM 15µg/strain/ 0.5mL Placebo: Phosphate-buffered saline Year 2007-08	RCT Randomized, observer blind	Age: 18-49 Sex: both (44-45% male) Healthy Country: USA, Finland, & Poland Setting: N/A Sample size Vaccine: 3676 Placebo: 3900	Follow-up: 21 days Seroconversion (CHMP) H1N1: 75% (71-78) H2N3: 68% (64-71) B: 68% (65-72) Seroprotection ($\geq 1:40$) H1N1: 98% (97-99) H3N2: 99% (98-100) B: 92% (90-94) GMTR H1N1: 14 (12,16) H3N2: 8.7 (7.7,9.7) B: 9.4 (8.4,10)	Rank: I Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95% CI)	Quality of Evidence
Tregnaghi MW, Stamboulia D, Vanadia PC, et al. (2012). Immunogenicity, safety, and tolerability of two trivalent subunit inactivated influenza vaccines: A phase III, observer-blind, randomized, controlled multicenter study. <i>Viral Immunology</i> , 25:216-225.	Agrippal & Fluvirin TIV, IM, 15µg/strain/ 0.5mL Year 2007-08 southern hemisphere	RCT, observer blind, phase III	Age: 18-64 (mean 38-39) Sex: both (36-44% male) Healthy Country: Argentina Setting: not stated Sample size Fluvirin: 232 Agriflu: 460	Day 21 blood sample Agrippal vs Fluvirin Seroconversion (4-fold rise) H1N1: 74 (69-78) vs 85 (79-89) H3N2: 72 (68-76) vs 88 (84-92) B 77 (73-81) vs 74 (68-79) Seroprotection ($\geq 1:40$) H1N1 93 (91-95) vs 99 (96-100) H3N2 96 (94-98) vs 100 (98-100) B 91 (88-94) vs 86 (81-90) GMTR H1N1: 12 (10-14) vs 27 (22-34) H3N2 : 10 (9-12) vs 22 (18-27) B 12 (10-13) vs 10 (8-12)	Rank: I Quality: Good
Ehrlich, HJ, Berezuk, G, Fritsch, S et al. (2012). Clinical development of a Vero cell culture-derived seasonal influenza vaccine. <i>Vaccine</i> , 30: 4377-4386	Fluzone TIV, IM 15µg/strain/ 0.5mL Comparator: Vero cell cultured vaccine (data not	RCT Double blind, multi-center	Age: 50-64 (mean 56) Sex: both (39.70% male) Healthy (immune suppressed and high risk excluded) Country: USA Setting: Research	Follow-up: 21 days Seroconversion (CHMP) H1N1 63.8 (57.1-70.1) H3N2 85.1 (79.7-89.5) B 62.9 (56.2-69.3) Seroprotection (CHMP) H1N1 86.9 (81.7-91.0) H3N2 95.9 (92.4-98.1)	Ranking: I Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95% CI)	Quality of Evidence
	ab- stracted)		Centers	B 93.7 (89.6-96.5)	
	Year		Sample size: 229	GMTR	
	2008-09			H1N1 6.9 (5.7-8.3)	
				H3N2 15.0 (12.4-18.3)	
				B 7.4 (6.1-8.9)	
Frenck, RW, Belshe, R, Brady, RC, et al. (2011) Comparison of the immunogenicity and safety of a split-virion, inactivated, trivalent influenza vaccine (Fluzone®) administered by intradermal and intramuscular route in healthy adults. <i>Vaccine</i> , 29 5666-5674.	Fluzone TIV,IM, 15µg/strain/0.5mL Intanza TIV,ID, 9µg/strain/0.1mL Year 2004-2005	RCT, partially blinded	Age: 18-49 and 50-64 Sex: both (32-34% male) Healthy volunteers (immune compromised not eligible) Country: USA Setting: Health Center Sample Size IM 18-49: 202 ID 18-49: 201 IM 50-64: 196 ID 50-64: 194	Follow-up: 21 days IM vs ID Seroprotection (EMEA) <u>18-49</u> year olds H1N1 92.5% vs 89.4% H3N2 100% vs 100% B 87.9% vs 84.8% <u>50-64</u> year olds H1N1 77.8% vs 72.4% H3N2 99.5% vs 99% B 74.4% vs 67.2% GMT <u>18-49</u> year olds H1N1 192 (162-228) vs 169 (147-217) H3N2 711 (623-813) vs 703 (612-808) B 109 (94-126) vs 113 (95-134) <u>50-64</u> year olds H1N1 75 (63-89) vs 74 (62-90) H3N2 492 (432-561) vs 535 (457-627) B 69 (59-80) vs 60 (51-71)	Rank I Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95% CI)	Quality of Evidence
Leroux-Roels I, Vets E, Freese R, et al. (2008). Seasonal influenza vaccine delivered by intradermal microinjection: A randomized controlled safety and immunogenicity trial in adults. <i>Vaccine</i> , 26:6614-6619.	Vaxigrip TIV, IM 15µg/ strain/ 0.5mL Intanza TIV, ID 9µg/ strain/ 0.1mL Year 2005- 2006	RCT, open label, multi- centre	Age: 18-58 (mean 40) Sex: both (36-37% male) Healthy volunteers (immune compromised not eligible) Countries: Germany, Belgium, Switzerland Setting: not specified Sample size TIV/IM: 379 TIV/ID: 381	Follow-up: 21 days ID vs IM Seroconversion (CHMP) H1N1 74.3 (69.7-78.7) vs 70.4 (65.6-74.9) H3N2 85.1 (81.2-88.5) vs 79.2 (74.8-83.1) B 76.4 (71.9-80.6) vs 73.5 (68.8-77.8) Seroprotection (≥1:40) H1N1 92.4 (89.3-94.9) vs 88.8 (85.3-91.8) H3N2 99.7 (98.6-100) vs 98.7 (97.0-99.6) B 90.6 (87.2-93.3) vs 85.5 (81.5-88.8) GMTR H1N1 16.2 (13.7-19.2) vs 13.8 (11.6-16.4) H3N2 28.2 (23.7-33.5) vs 20.7 (17.5-24.4) B 12.1 (10.5-13.8) vs 10.8 (9.6-12.3)	Rank: I Quality: Good
Coleman BL, McGeer AJ, Halperin SA, et al. (2012). A randomized control trial comparing immunogenicity, safety, and preference for self- versus nurse-administered intradermal influenza	Intanza TIV, ID 9µg/ strain/ 0.1mL Season 2010- 2011	RCT, open label, multi- centre	Age: 18-59 Sex: both 29.80% male Healthy Country: Canada Setting: Acute care hospitals & community Sample size:	Follow-up: 21 days: all participants Seroconversion (CHMP) H1N1 61.4 (55.0-67.6) H3N2 65.6 (59.5-71.8) B 39.9 (33.6-46.3) Seroprotection (≥1:40) H1N1 97.4 (95.3-99.4) H3N2 97.8 (95.9-99.7) B 100	Rank: I Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95% CI)	Quality of Evidence
vaccine. <i>Vaccine</i> , 30: 6287-6293.			113 Nurse-administered 115 Self-administered	GMTR H1N1 6.6 (5.8-7.5) H3N2 10.2 (8.8-11.9) B 4.1 (3.7-4.7)	
Live Attenuated Influenza Vaccine (LAIV)					
Atmar RL, Keitel WA, Cate TR et al. (2007). A dose-response evaluation of inactivated influenza vaccine given intranasally and intramuscularly to healthy young adults. <i>Vaccine</i> 25: 5367-5373	Fluzone TIV, IM 15µg/strain/0.5mL FluMist LAIV, IN Placebo: Saline Years: 2001-2002	RCT, double blind, randomized	Age: 18-45 (mean 29) Sex: both (44% male) Healthy Country: USA Setting: Health center Sample size: LAIV 21 TIV 21 Placebo 42	Follow-up: 28 days TIV vs LAIV Seroconversion (4 fold rise) H1N1: 52 vs 48% H3N2: 57 vs 29% B: 62 vs 14% GMT H1N1: 5.2 (2.5-11) vs 3.1 (1.6-5.9) H3N2: 3.9 (2.1-7.2) vs 2.1 (1.4-3.1) B: 3.2 (1.9-5.3) vs 1.3 (0.9-1.7)	Rank: I Quality: Good
Block, S.L, Yogev, R., Hayden, F.G., et al. (2008). Shedding and immunogenicity of live attenuated influenza vaccine virus in subjects 5-49 years of age. <i>Vaccine</i> , 26: 4940-4946.	FluMist 10 ⁷ TCID ₅₀ /0.5mL Year: 2004-2005	Cohort, open-label, single arm, multi-center, phase IV	Age: 18-49 (mean 30) Sex: both (37.4% male) Healthy volunteers Country: USA Setting: Health center Sample size: 115	Follow-up: 28 days Seroconversion (4-fold rise) H1N1 26.1 (18.3,35.1) H3N2 25.2 (17.6,34.2) B 12.2 (6.8,19.6) GMT ratio H1N1 2.0 (1.7-2.3) H3N2 2.2 (1.9-2.4) B 1.4 (1.2-1.5)	Rank: II-2 Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95% CI)	Quality of Evidence
Ohmit SE, Victor JC, Rotthoff JR, et al. (2006). Prevention of antigenically drifted influenza by inactivated and live attenuated vaccines, <i>NEJM</i> , 355(24): 2513-2522.	Fluzone TIV, IM 15µg/ strain; 0.5mL FluMist LAIV, IN 0.5mL Season 2004- 2005	RCT double blind, multi- centre	Age: 18-46 (mean 27) Sex: both (38% male) Healthy Country: USA Setting: University & Community Sample size TIV: 519 LAIV: 522	Follow-up: 30 days TIV vs LAIV Seroconversion (4-fold rise in HAI titres) H1N1 70.3 vs 8.5% H3N2 66.7 vs 22.2 B strain 85.2 vs 13.5	Rank: I Quality: Good
Ohmit SE, Victor JC, Teich ER, et al. (2008). Prevention of symptomatic seasonal influenza in 2005-2006 by inactivated and live attenuated vaccines, <i>Journal of Infectious Diseases</i> , 198(1):312-317.	Fluzone TIV, IM, 15µg/ strain; 5mL FluMist LAIV, IN 0.5mL Year: 2005- 2006 Placebo: Saline	RCT double blind, multi- centre	Age: 18-48 (mean 25) Sex: both (40% male) Healthy Country: USA Setting: University & community Sample size TIV: 445 LAIV: 431	Follow-up: 30 days Fluzone vs FluMist Seroconversion (4-fold rise in HAI titres) H1N1 51.6 vs 9.7 H3N2 76.5 vs 20.4 B strain 57.2 vs 20.0	Rank: I Quality: Good
Ohmit SE, Petrie JG, Cross RT, et al. (2011). Influenza hemagglutination	Fluzone TIV, IM, 15µg/ strain; 0.5mL	RCT double blind, multi- centre	Age: 18-49 Sex: both Healthy Country: USA	Follow-up: 30 days Fluzone vs FluMist Seroconversion (4-fold rise)	Rank: I Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95% CI)	Quality of Evidence
n-inhibition antibody titer as a correlate of vaccine-induced protection. <i>J Infect Dis</i> , 204: 1879-1885.	FluMist LAIV, IN Year: 2007-2008 Placebo: Saline		Sample size TIV: 259 LAIV: 289	H3N2 76.4 vs 21.1% Seroprotection H3N2 $\geq 1:32$ 100 vs 84.8 H3N2 $\geq 1:64$ 97.3 vs 70.6 GMTR H3N2 7.6 vs 4.9	
Ramakrishnan, A., Althoff, K.N., Lopez, J.A., et al.(2012). Differential serum cytokine responses to inactivated and live attenuated seasonal influenza vaccines. <i>Cytokine</i> , 60: 661-666.	Fluzone TIV, IM 15µg/strain/ 0.5mL FluMist LAIV, IN Years 2006-2007 2007-2008	Cohort, convenience sample	Age: 18-49 (mean 29-30) Sex: both (40% female) Healthy employees, no immune compromised Country: USA Setting: Hospital Sample size 2006-07 TIV: 25 LAIV: 17 2007-08 TIV: 31 LAIV: 21	Follow-up: 28 days Fluzone vs FluMist <u>2006-2007</u> Seroconversion (4-fold rise) H1N1 36 vs 0% H3N2 68 vs 18% B 56 vs 12% <u>2007-2008</u> Seroconversion (4-fold rise) H1N1 45 vs 0% H3N2 52 vs 29% B 23 vs 5% Serum cytokines (IL-8 and TNF- α) did not increase after LAIV administration	Rank: II-2 Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95% CI)	Quality of Evidence
Davidson LE, Fiorino AM, Snyderman DR, Hiberd PL (2011). Lactobacillus GG as an immune adjuvant for live-attenuated influenza vaccine in healthy adults: a randomized double-blind placebo-controlled trial. <i>Eur J Clin Nutr</i> 65: 501-507	FluMist LAIV, IN 0.2mL Year: 2007-2008 Concomittant : oral probiotic (Lactobacillus GG) or gelatin placebo	RCT double blind	Age: 18-48 (mean 33) Sex: both 38% male Country: USA Setting: Community Healthy Sample Size: 20 vaccine & placebo 19 vaccine & probiotic	Follow-up: day 14, 28, or 56 (as chosen by author) Vaccine vs vaccine with probiotic Seroconversion (CHMP) H1N1 8 (0-38) vs 27 (6-61), NS H3N2 63 (24-91) vs 33 (10-65), NS B 42 (15-72) vs 40 (16-68), NS Seroprotection ($\geq 1:40$) H1N1 42 (20-67) vs 50 (27-73), NS H3N2 84 (60-97) vs 55 (32-77), NS B 53 (29-76) vs 45 (23-68), NS GMTR H1N1 1.2 vs 1.1, NS H3N2 1.6 vs 1.8, NS B 1.2 vs 1.3, NS	Rank: I Quality: Fair (follow up was unclear)
Ramakrishnan, A., Althoff, K.N., Lopez, J.A., et al.(2012). Differential serum cytokine responses to inactivated and live attenuated seasonal influenza vaccines. <i>Cytokine</i> , 60: 661-666.	Fluzone TIV, IM 15µg/strain/0.5mL FluMist LAIV, IN Years 2006-	Cohort, convenience sample	Age: 18-49 (mean 29-30) Sex: both (40% female) Healthy employees, no immune compromised Country: USA Setting: Hospital	Follow-up: 28 days Fluzone vs FluMist <u>2006-2007</u> Seroconversion (4-fold rise) H1N1 36 vs 0% H3N2 68 vs 18% B 56 vs 12% <u>2007-2008</u> Seroconversion (4-fold rise)	Rank: II-2 Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95% CI)	Quality of Evidence
	2007 2007-2008		Sample size 2006-07 TIV: 25 LAIV: 17 2007-08 TIV: 31 LAIV: 21	H1N1 45 vs 0% H3N2 52 vs 29% B 23 vs 5% Serum cytokines (IL-8 and TNF- α) did not increase after LAIV administration	
Couch RB, Atmar RL, Keitel WA, et al. (2012). Randomized comparative study of the serum anti-hemagglutinin and anti-neuraminidase antibody responses to six licensed trivalent influenza vaccines. <i>Vaccine</i> 31: 190-195	Afluria, Fluarix, Flulaval, Fluvirin, Fluzone TIV, IM 15 μ g/strain/0.5mL FluMist LAIV, IN Year: 2008-09	RCT, Subjects blinded to specific TIV, but not to TIV vs LAIV; all clinical personnel and lab techs blinded except vaccinator	Age: 18-40 Sex: both 50% male Healthy Country: USA Setting: Health Center Sample Size: 30 per vaccine group	Follow-up: 28 days Afluria vs Fluarix vs Flulaval vs Fluvirin vs Fluzone vs FluMist Seroconversion (4-fold rise in HI titres) H1N1: 47 vs 63 vs 43 vs 57 vs 47 vs 7 H3N2: 57 vs 60 vs 67 vs 73 vs 50 vs 3 B: 37 vs 30 vs 20 vs 37 vs 33 vs 3 GMTR (HI titres) H1N1: 2.2 vs 2.6 vs 2.2 vs 2.6 vs 2.0 vs 0.4 H3N2: 2.6 vs 2.6 vs 2.7 vs 3.2 vs 2.4 vs 0.4 B: 1.9 vs 1.6 vs 1.8 vs 1.8 vs 1.8 vs 0.4 Geometric mean serum neutralizing antibody titre increase H1N1: 4.0 vs 4.6 vs 3.9 vs 3.6 vs 5.1 vs 0.9 H3N2: 3.5 vs 3.1 vs 4.0 vs 3.6 vs 4.3 vs 0.3 B: 2.7 vs 2.7 vs 2.8 vs 3.0 vs 3.0 vs 0.4	Rank: I Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95% CI)	Quality of Evidence
				Neuraminidase-inhibition antibody titres mean fold increases N1: 1.26 vs 0.66 vs 0.61 vs 1.02 vs 1.02 vs 0.47 N2: 1.14 vs 2.04 vs 1.71 vs 1.25 vs 1.65 vs 0.17	
Barria, M.I., Garrido, J.L., Stein, C., et al. (2013). Localized Mucosal Response to Intranasal Live Attenuated Influenza Vaccine in Adults. <i>Journal of Infectious Diseases</i> , 207:115-124.	FluMist 2mL, IN Year 2010-2011	Cohort	Age: 18-49 (mean 30) Sex: both (65% male) Healthy employees Country: USA Setting: Hospital Sample size Vaccinated: 79	H1N1 only 4-fold rise in serum HAI Day 1 compared with day 3: 9% 2-fold rise in IgA titres from nasal wash (ELISA) Day 3 compared with day 30: 33%	Rank: II-2 Quality: Good
Concomitant administration					
Weston, W.M., Chandrashekar, V., Friedland, L.R., et al. (2009). Safety and immunogenicity of a tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine when co-administered with influenza	Fluvirix, TIV, IM 15µg/strain/0.5mL Boostrix Tdap 0.5mL Administered concurrently or serially (30 days)	RCT, unblinded	Age: 19-64 (mean 46) Sex: both (42% male) Healthy volunteers Country: USA Setting: Health center Sample size Concurrent 748 Serial 749	Follow-up: 30 days Concurrent vs serial vaccination Seroconversion (CHMP) H1N1: 58.5 (55-62) vs 56.1 (52-60) H3N2: 79.1 (76-82) vs 73.5 (70-77) B: 65.4 (62-69) vs 63.2 (59-67) Seroprotection (≥1:40) H1N1: 94.1 (92-96) vs 95.3	Rank: I Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Immunogenicity Findings (95% CI)	Quality of Evidence
vaccine in adults. <i>Human Vaccines</i> , 5:858-866.	post TIV Year 2006-07			(93-97) H3N2: 97.6 (96-99) vs 98.2 (97-99) B: 96.3 (95-98) vs 96.9 (95-98) GMTR H1N1: 7.3 vs 6.6 H3N2: 13.6 vs 11.6 B: 7.1 vs 6.0	
Kerzner B, Murray AV, Cheng E, et al. (2007). Safety and immunogenicity profile of the concomitant administration of Zostavax and inactivated influenza vaccine in adults aged 50 and older. <i>Journal of the American Geriatrics Society</i> , 55:1499-1507.	Fluzone or Vaxigrip TIV, IM 15µg/strain/ 0.5mL Zostavax or placebo opposite arm (or 4 week delay) Year 2005-2006	RCT, blinded, placebo controlled	Age: 50+ (50-59 abstracted) Sex: both (43-44% male) Health: no immune compromising diseases Countries: USA, Germany, UK, Italy, Netherlands Setting: not specified Sample size (50-59 yrs) Concomitant: 129 Serial: 130	Follow-up: 28 days Concomitant vs serial vaccinations GMFR Influenza H1N1 7.3 (5.5-9.8) vs 6.8 (5.1-9.0) H3N2 12.2 (9.3-16) vs 10.0 (7.9-13.0) B 9.0 (6.8-11.9) vs 8.6 (6.9-10.8) Zostavax 2.4 (2.0-2.8) vs 2.4 (2.0-2.8)	Rank: I Quality: Good

AR: attack rate

ARI: acute respiratory illness

CHMP: European Committee for Medical Products for Human Use

GMT: geometric mean titer

GMTR: geometric mean titer ratio

GMFR: geometric mean fold rise

GP: general practitioner

ILI: influenza-like illness

IM: intramuscular

ID: intradermal

IN: intranasal

LAIV: live attenuated influenza virus

NOS: not otherwise specified

OR: odds ratio

PCR: polymerase chain reaction

RCT: randomized controlled trial

RR: relative risk

TIV: trivalent inactivated (influenza) vaccine

VE: vaccine effectiveness

vs: versus

APPENDIX C: EVIDENCE TABLE OF VACCINE SAFETY AND IMMUNOGENICITY

Study	Vaccine	Study Design	Participants	Summary of Safety Findings (95% CI)	Quality of Evidence
Trivalent Inactive Influenza Vaccines (TIV)					
Frey S, Poland G, Percell S, Podda A. (2003). Comparison of the safety, tolerability, and immunogenicity of a MF59-adjuvanted influenza vaccine and a non-adjuvanted influenza vaccine in non-elderly adults. <i>Vaccine</i> 21:4234-4237	Fluzone TIV, IM 15µg/strain/0.5mL Years 1995-96 and 1996-97 Comparator: Fluad (adjuvanted; not abstracted)	RCT, randomized, observer blind	Age: 18-65 Sex: both Country: USA Healthy Sample size: Season 1: 151 Season 2: 96 (same vaccine/placebo administered in 2 nd season as first)	Reactogenicity 7 day active (diaries) follow-up Season 1 vs season 2 Arm pain 64 vs 69 Arm redness 22 vs 29 Induration 17 vs 26 Warmth, site 18 vs; 21 Muscle aches 6 vs 6 Arthralgia 0 vs 0 Headache 21 vs 16 Malaise 8 vs 1 Fever 0 vs 1 Chills 1 vs 1 Serious adverse event 6 month follow-up; None reported	Rank: I Quality: Good
Duque, Moreno, Hurtado et al. (2001). Effectiveness of an anti-flu vaccine in a Colombian labor population. <i>Pan American Journal of Public Health</i>	Agrippal (Agriflu) TIV, IM 0.5mL Year 1997-98 Placebo: vitamin C	RCT double blind	Age: 18-60 Sex: both (24% male) Healthy Country: Columbia Setting: Work sites Sample size: 247 vaccine	3 day active follow-up Reactogenicity Vaccine vs. placebo Arm pain 51.8 vs 54.1%, NS Arm redness 3.2 vs 0.4, p=0.02 Swelling 3.6 vs 0.8, p=0.03 Headache 13 vs 11.8, NS Malaise 20.2 vs 20.7,	Rank: I Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Safety Findings (95% CI)	Quality of Evidence
			246 placebo	NS Fever 3.2 vs 1.6%, NS Serious adverse events Not reported	
Samad, A.H., Usul, M., Zakaria, D., et al. (2006). Workplace vaccination against influenza in Malaysia: Does the employer benefit? <i>Journal of Occupational Health</i> , 48: 1-10.	Vaxigrip TIV, IM 15µg/strain/ 0.5mL Year 2000-2001	Cohort, prospective	Age: 18-64 (mean 32-33) Sex: both (80% male) Healthy employees, excluded chronic diseases Country: Malaysia Setting: Company Sample size: 1022 504 vaccinated 518 not vaccinated	Reactogenicity 7 day active follow-up Arm Pain 5.8% Redness 1.8% Swelling 1.4% Sore throat 7.5% Fever 8.9% Fatigue 7.3% Malaise 5.2% Chills 1.8% Cough 5.4% Runny nose 8.7% Itching 1.6% Myalgia 3.8% Headache 4.6% Serious adverse events None reported	Rank: II-2 Quality: Good
Belshe RB, Newman FK, Cannon J. (2004). Serum antibody responses after intradermal vaccination against influenza. <i>New England</i>	Fluzone TIV, IM 15µg/strain/ 0.5mL Comparator: Un-	RCT, open label	Age: 18-60 (mean 39) Sex: both (37% male) Healthy Country: USA Setting: Health Centers	Reactogenicity 7 day active follow-up IM vs ID Arm pain: 67 vs 45%, NS Arm redness: 6 vs 88 p<0.01 Swelling: 9 vs 52	Rank: I Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Safety Findings (95% CI)	Quality of Evidence
<i>Journal of Medicine</i> , 351:2286-2294.	licensed TIV, ID 0.6µg/ strain (not ab- stracted) Year 2001- 2002		Sample size: Fluzone 69 Comparator 61 Total 130	p<0.01 Lump: 6 vs 75 p<0.01 Serious Adverse Events None reported	
Engler, RJM, Nelson, MR, Klote, MM et al. (2008). Half- vs full-dose trivalent inactivated influenza vaccine (2004-2005): Age, dose, and sex effects on immune responses. <i>Arch Intern Med</i> . 168(22): 2405-14	Fluzone TIV, IM 15µg/ strain/ 0.5mL Year 2004-05 Compara- tor: full vs half dose (only full dose re- viewed)	RCT Single blinded	Age: 18-64 Sex: both (56% male) Healthy Country: UK Setting: Health Centers Sample Size: 628	Reactogenicity 21 day active (diaries) follow-up Arm pain 5.9% Arm redness 13.4 Lump 2.7 Numbness 9.7 /burning Muscle aches 4.5 Joint pain 4.5 Headache 5.9 Fatigue 6.8 ILI 3.5 Serious adverse events 5 month follow-up 3 hospitalizations, considered unrelated	Rank: I Quality: Good
Frenck RW, Belshe, R, Brady, RC, et al. (2011). Comparison of the immunogenicity and safety of a	Fluzone TIV, IM 15µg/ strain/ 0.5mL	RCT, partially blinded,	Age: 18-49 Sex: both (32- 34% male) Healthy volunteers (immune compromised not	Reactogenicity 7 day active follow-up IM vs ID Redness: 3% vs 74%	Rank I Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Safety Findings (95% CI)	Quality of Evidence
split-virion, inactivated, trivalent influenza vaccine (Fluzone) administered by intradermal and intramuscular route in healthy adults. <i>Vaccine</i> , 29 5666-5674.	Intanza TIV, ID 9µg/strain/ 0.1mL Year 2004-2005		eligible) Setting: Health Center Country: USA Sample Size IM 202 ID 201	Site Swelling: 1.3% vs 27% Headaches: 25% vs 31% Serious adverse events 6 month follow-up 1 per group: 1 acute disseminated encephalomyelitis one month post-ID vaccination considered possibly related	
Treanor JJ, Campbell JD, Brady RC, et al. (2005). Rapid licensure of a new, inactivated influenza vaccine in the United States. <i>Human Vaccines</i> , 1:239-244	Fluarix TIV, IM 15µg/strain/ 0.5mL Placebo: Saline Year 2004-2005	RCT, double blind	Age: 18-64 (mean 39) Sex: both Healthy volunteers Country: USA Setting: not stated Sample size Vaccinated: 535 (18-49) 210 (50-64) Placebo: 190	Reactogenicity 3 day active follow-up Vaccine vs placebo Arm pain 55 (51-58) vs 12 (8-17) (p < 0.001) Redness 17 (15-20) vs 10 (7-16) (p = 0.016) Swelling 9 (7-12) vs 6 (3-10) Myalgia 23 (20-26) vs 12 (8-17) (p = 0.001) Arthralgia 6 (5-8) vs 12 (8-17) Headache 19 (17-22) vs 21 (16-28) Fever 1.7 (1-3) vs 1.6 (0-4) Chills 3 (2-5) vs 3 (1-6) Serious adverse events 21 day passive follow-up 1 reported (cardiovascular disease), 17 days after vaccination, considered unrelated	Rank: I Quality: Good
At'kov, O.Y., Azarov, A.V.,	Vaxigrip	Cohort, pro-	Age: 18-64 (mean	Reactogenicity	Rank: II-2

Study	Vaccine	Study Design	Participants	Summary of Safety Findings (95% CI)	Quality of Evidence
Zhukov, D.A., et al. (2011). Influenza vaccination in healthy working adults in Russia: observational study of effectiveness and return on investment for the employer, <i>Applied health economics and health policy</i> , 9: 89-99.	TIV, IM 15µg/strain/ 0.5mL Year 2005-2006	spective	39) Sex: both (55% male) Healthy employees Country: Russia Setting: transport company Sample size Vaccinated: 701 Unvaccinated: 630	7 day active follow-up Arm pain 6.6% Arm redness 3.6% Headache 3.3% Malaise 4.3% Fatigue 2.9% Runny nose 3.0% Any 18% HCP visit 17.5% Serious adverse events None reported	Quality: Good
Beran J, Wertzova V, Honegr K, et al. (2009). Challenge of conducting a placebo-controlled randomized efficacy study for influenza vaccine in a season with low attack rate and a mismatched vaccine B strain: a concrete example. <i>BMC Infectious Diseases</i> , 9:1-11	Fluarix TIV, IM 15µg/strain/ 0.5ml Placebo Saline Year 2005-2006	RCT, double blinded	Ages: 18-64 (mean age:39) Sex: both Healthy volunteers Country: Czech Republic Setting: not stated Sample Size Vaccine: 632	Reactogenicity 21 day active follow up vaccine vs placebo Arm redness 1.7% Swelling 2.3 Fatigue 23.4 vs 15.9 AE: both groups 2.3% reported 0 vaccine related	Rank I Quality: Good
Durando P, Fenoglio D, Boschini A, et al. (2008). Safety and immunogenicity of two influenza	Agrippal TIV, IM 15µg/strain/ 0.5mL	RCT No blinding	Age: 18-65 (mean 32) Sex: both (89% male) Healthy (seronegative for	4 day active (diary) follow-up Reactogenicity Arm pain 23.7% Arm redness 2.5	Rank: I Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Safety Findings (95% CI)	Quality of Evidence
virus subunit vaccines, with or without MF59 adjuvant, administered to human immunodeficiency virus Type 1-seropositive and -seronegative adults. <i>Clinical and Vaccine Immunology</i> , 15(2): 253-259.	Comparison Fluad, adjuvanted (not abstracted) Year 2005-2006		HIV-1) Country: Italy Setting: Health Center Sample size: TIV: 80	Induration 6.2 Muscle aches 6.2 Arthralgia 7.5 Headache 10.0 Malaise 16.2 Weakness 6.2 Sweating 5.0 Shivering 8.7 Fever 5.0 Serious adverse events None reported	
Leroux-Roels I, Vets E, Freese R, et al. (2008). Seasonal influenza vaccine delivered by intradermal microinjection: A randomized controlled safety and immunogenicity trial in adults. <i>Vaccine</i> , 26:6614-6619.	Vaxigrip TIV, IM 15µg/strain/ 0.5mL Intanza TIV, ID 9µg/strain/ 0.1mL Year 2005-2006	RCT, open label, multi-centre	Age: 18-58 (mean 40) Sex: both (36-37% male) Healthy volunteers (immune compromised not eligible) Countries: Germany, Belgium, Switzerland Setting: not specified Sample size IM: 390 ID: 588	Reactogenicity 7 day active (diary) follow-up IM vs ID Bruising 2.3 (1.1-4.3) vs 1.5 (0.7-2.9) Fever 0.8 (0.2-2.2) vs 1.5 (0.7-2.9) Malaise 14.4 (11.-18.2) vs 11.6 (9.1-14.4) Shivering 7.4 (5.0-10.5) vs 6.0 (4.2-8.2) Serious adverse events 7 reported, 6 judged as unrelated to vaccination 1 peritonsillar abscess post ID-vaccination judged as possibly related	Rank: I Quality: Good
Jackson LA, Gaglani MJ, Keyserling HL et	Flulaval TIV, IM	RCT Randomized,	Age: 18-49 Mean: 32.7	Reactogenicity , both seasons combined	Rank: I Quality:

Study	Vaccine	Study Design	Participants	Summary of Safety Findings (95% CI)	Quality of Evidence
al. (2010) Safety, efficacy, and immunogenicity of an inactivated influenza vaccine in healthy adults: a randomized, placebo-controlled trial over two influenza seasons. <i>BMC Infectious Diseases</i> 10(71)	15µg/strain/ 0.5mL Placebo: saline 2005-2007 Mis-match strain – B lineage	double blind (administering nurse not blinded)	Healthy Setting: Health Center Sex: Both (40% male) Country: USA Sample size 3714 vaccine 3798 placebo	3 day active follow-up TIV vs placebo Arm pain 51 vs 14 (p<0.0001) Arm redness 13 vs 6 (p<0.0001) Swelling 11 vs 3 (p<0.0001) Muscle aches 18 vs 10 (p<0.0001) Headache 18 vs 19, NS Fatigue 20 vs 18 (p=0.005) Fever 3 vs 1 (p=0.005) Chills 4 vs 4, NS Cough 8 vs 7, NS Trouble breathing 3 vs 3, NS Serious adverse events 4.5 months passive follow-up Vaccine 1%; Placebo 1%, NOS	Good
Belshe, R.B., Newman, F.K., Wilkins, K., et al. (2007). Comparative immunogenicity of trivalent influenza vaccine administered by intradermal or intramuscular route in healthy adults. <i>Vaccine</i> , 25:6755-6763.	Fluzone, TIV, IM 15µg/strain/ 0.5mL Season 2006-2007	RCT, open label	Age: 18-50 (mean 28-32) Sex: both (19% male) Healthy (immunosuppressed or pregnant not eligible) Country: USA Setting: Health centers Sample size	7 day active follow-up Reactogenicity Arm pain 49% Redness 26% Swelling 22% Muscle ache 32% Headache 48% Malaise 26% Fever 3%	Rank: I Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Safety Findings (95% CI)	Quality of Evidence
			TIV: 31	Serious adverse events None reported	
Van Damme, P., Oosterhuis-Kafeja, F., Van der Wielen, M., et al. (2009). Safety and efficacy of a novel microneedle device for dose sparing intradermal influenza vaccination in healthy adults. <i>Vaccine</i> , 27:454-459.	α-RIX TIV, IM 15µg/strain/0.5mL Comparison αRIX, 0.1 and 0.2mL (not abstracted) Year 2006-2007	RCT Single blind	Age: 18-40 (mean 27) Sex: both (44% male) Healthy volunteers, high risk excluded Country: Belgium Setting: University Sample size α-RIX: 60	Reactogenicity 7-day active follow-up Arm pain 70% Redness 25% Swelling 12% Lump 18% Bruising 1.7% Serious adverse events None reported	Rank: I Quality: Good
Weston, W.M., Chandrashekar, V., Friedland, L.R., et al. (2009). Safety and immunogenicity of a tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine when co-administered with influenza vaccine in adults. <i>Human Vaccines</i> , 5:858-866.	Fluvirix, TIV, IM 15µg/strain/0.5mL Boostrix Tdap 0.5mL (diphtheria, tetanus, pertussis) Administered concurrently or serially (30 days)	RCT, unblinded	Age: 19-64 (mean 46) Sex: both (42% male) Healthy volunteers Country: USA Setting: Health center Sample size Concurrent 748 Serial 749	Reactogenicity 60 day follow-up Concurrent vs serial 21.5 vs 27.4% reported unsolicited reactions 7 vs 6.1% considered vaccine related Serious adverse events 2 concurrent, 7 serial 1 vaccine related (serial): chest pain, dyspnea and headache on the day of vaccination with TIV	Rank: I Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Safety Findings (95% CI)	Quality of Evidence
	post TIV)				
	Year 2006-07				
Tregnaghi, M.W., Stamboulia, D., Vanadia, P.C., et al. (2012). Immunogenicity, Safety, and Tolerability of Two Trivalent Subunit Inactivated Influenza Vaccines: A Phase III, Observer-Blind, Randomized, Controlled Multicenter Study. <i>Viral Immunology</i> , 25:216-225.	Agrippal & Fluvirin TIV, IM, 15µg/ strain/ 0.5 mL Year 2007 southern hemi- sphere	RCT, observer blind, phase III	Age: 18-64 (mean 38-39) Sex: both (36-44% male) Healthy Country: Argentina Setting: not stated Sample size Fluvirin: 232 Agriflu: 460	Reactogenicity 7-day active (diary) follow-up Agriflu vs Fluvirin Arm pain 25 vs 30% Redness 6 vs 5 Lump 8 vs 10 Swelling 6 vs 6 Bruising 5 vs 6 Headache 23 vs 18 Fatigue 10 vs 10 Fever 2 vs 3 Chills 5 vs 7 Malaise 12 vs 12 Myalgia 14 vs 16 Arthralgia 7 vs 6 Sweating 5 vs 5 Serious adverse events 6 month follow-up Agriflu vs Fluvirin: 8 vs 2 1 possibly related (spontaneous abortion 8 weeks post-Agriflu vaccination)	Rank: I Quality: Good
Baxter R, Patriarca PA, Ensor K, et al. (2011). Evaluation of the safety, reactogenicity	Fluzone, TIV, IM 15µg/ strain/ 0.5mL	RCT, observer blinded	Age: 50-64 (mean 56) Sex: both (36% male) Healthy (acute & chronic illness not	Reactogenicity 7 day active follow-up Arm pain 55% Redness 8%	Rank: I Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Safety Findings (95% CI)	Quality of Evidence
and immunogenicity of FluBlok (R) trivalent recombinant baculovirus-expressed hemagglutinin influenza vaccine administered intramuscularly to healthy adults 50-64 years of age. <i>Vaccine</i> , 29:2272-2278.	Un-licensed recombinant TIV (not abstracted) Season 2007-2008		eligible) Country: USA Setting: Health centers Sample size TIV: 302	Swelling 10% Bruising 5% Muscle ache 13% Arthralgia 7% Headache 21% Fatigue 19% Chills 5% Serious adverse events 6 month follow-up One cerebrovascular accident and one prostate cancer; neither vaccine related	
Frey S, Vesikari T, Szymczakiewicz-Multanowska A, et al. (2010). Clinical Efficacy of Cell Culture-Derived and Egg-Derived Inactivated Subunit Influenza Vaccines in Healthy Adults. <i>Clinical Infectious Diseases</i> 51(9):997-1004	Agripal (Agriflu) TIV, IM 15µg/strain/0.5mL Year 2007-08 Placebo: Phosphate-buffered saline	RCT Randomized, observer blind	Age: 18-49 (mean 33) Sex: both (44-45% male) Healthy Country: USA, Finland, Poland Vaccine: 3676 Placebo: 3900	Reactogenicity 7 day active (diaries) follow-up TIV vs placebo Arm pain 23 vs 10 Arm redness 13 vs 10 Muscle aches 10 vs 7 Headache 15 vs 15 Malaise 7 vs 6 Fatigue 11 vs 10 Serious adverse events 180 day follow-up Vaccine: 1 death; Placebo: 1 death Not attributed to vaccination	Rank: I Quality: Good
Ehrlich, HJ, Berezuk, G, Fritsch, S et al. (2012). Clinical development of	Fluzone TIV, IM 15µg/strain/	RCT Double blind, multi-	Age: 50-64 (mean 56) Sex: both (40% male)	Reactogenicity 7 days active (diary) follow-up Arm pain 30.1% (24.3-	Rank: I Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Safety Findings (95% CI)	Quality of Evidence
a Vero cell culture-derived seasonal influenza vaccine. <i>Vaccine</i> , 30: 4377-4386	0.5mL Comparator: Vero-cell cultured vaccine (data not abstracted) Year 2008-09	center	Healthy (immune suppressed and high risk excluded) Country: USA Setting: Research Centers Sample size: 229	36.5) Arm redness 2.6 (1.0-5.6) Swelling 2.2 (0.7-5.0) Induration 3.1 (1.2-6.2) Muscle aches 11.8 (7.9-16.7) Joint pain 5.7 (3.1-9.5) Headache 14.4 (10.1-19.6) Malaise 11.8 (7.9-16.7) Fatigue 13.5 (9.4-18.7) Sweating 2.2 (0.7-5.0) Fever 1.3 (0.3-3.8) Chills 3.9 (1.8-7.3) Cough 0.4 (0.0-2.4) Serious adverse events 1 reported, no details provided	
Coleman BL, McGeer AJ, Halperin SA, et al. (2012). A randomized control trial comparing immunogenicity, safety, and preference for self- versus nurse-administered intradermal influenza vaccine. <i>Vaccine</i> , 30: 6287-6293.	Intanza TIV, ID 9µg/ 0.1mL Season 2010-2011	RCT, open label, multi-centre, lab-blinded	Age: 18-59 Sex: both 29.80% male Healthy Country: Canada Setting: Acute care hospitals & community Sample size: 115 nurse administered 113 self-administered	Reactogenicity 7 day, active (diary) follow-up Nurse-administered vs. self-administered Arm pain 60 vs. 62% Arm redness 94 vs. 95 Swelling 65 vs. 68 Induration 70 vs. 69 Muscle aches 31 vs. 23 Joint pain 12 vs. 9 Headache 28 vs. 28 Malaise 27 vs. 26 Fatigue 31 vs. 29 Sweating 8 vs. 5	Rank: I Quality: Good

Study	Vaccine	Study Design	Participants	Summary of Safety Findings (95% CI)	Quality of Evidence
				Fever 1 vs. 1 Itching, arm 11 (overall) Serious adverse events None reported	

AR: attack rate

ARI: acute respiratory illness

CHMP: European Committee for Medical Products for Human Use

GBS: Guillain Barré Syndrome

GMT: geometric mean titer

GMTR: geometric mean titer ratio

GP: general practitioner

ILI: influenza-like illness

IM: intramuscular

ID: intradermal

IN: intranasal

LAIV: live attenuated influenza virus

NOS: not otherwise specified

OR: odds ratio

PCR: polymerase chain reaction

RCT: randomized controlled trial

RR: relative risk

TIV: trivalent inactivated (influenza) vaccine

VE: vaccine effectiveness

vs: versus

APPENDIX D: SEARCH STRATEGY AND RESULTS

The literature search was conducted in three databases: Web of Science, Medline and EMBASE. The search strategy was designed with the keywords and limits intended to capture all the articles in these databases that were relevant to the systematic review's disease, interventions, outcomes, population and time period of interest ([Table 1](#)). This search strategy was applied to all three databases on November 9, 2012 to capture records published since January 1, 2000. The search yielded 3376, 3792 and 3332 records from Web of Science, Medline and EMBASE respectively for a total of 10,500 records. The search strategy was then reapplied to all three databases on February 5, 2013 to capture records published since the November 9, 2012 search. The second search yielded 43, 440 and 603 records from Web of Science, Medline and EMBASE respectively for a total of 1086 records. Two other records were added from the reference lists of review articles. This concluded the search for applicable records ([Figure 1](#)).

After combining the records of both searches with articles found from reference lists and removing duplicates, 9401 records remained and their titles and abstracts were screened for relevance. Records were excluded at this stage of screening if it was clear from their title and abstract that their study population did not contain at least some proportion of healthy adults ages 19 to 64 who were not pregnant. Records were also excluded if it was clear that they were not influenza vaccine-related or if it was clear that they were solely focused on pandemic influenza, quadrivalent, virosomal or whole vaccines and did not investigate season influenza in any analyses. Finally, records were excluded if it was clear that their outcomes did not include: laboratory-confirmed influenza, influenza-like illness, clinic/physician visit, hospitalization, influenza-related mortality, absenteeism, days of work/school missed due to illness or economic impact of illness. Upon applying these criteria, 9124 records were excluded. The remaining records were retrieved for full-text review but 26 were not available.

Each of the 251 articles retrieved for full-text review were critically appraised. Articles were only excluded if they were assessed as ineligible by two independent reviewers. If upon first review the article was assessed as ineligible, the article was reviewed by a second reviewer. If the first and second reviewers did not agree on the article's eligibility, the article was assessed by a third reviewer.

Articles were designated as ineligible by reviewers if they had greater than 10% of their study population either outside the 19-64 range or with high risk conditions. High risk conditions included any diseases or conditions known to alter the effectiveness, immune response or safety of the vaccine; for example, chronic diseases, pregnancy and immunocompromising diseases and conditions. Articles were also excluded if they did not present some data, whether through sub-group analyses or otherwise, that were exclusive to the intervention of interest: seasonal trivalent influenza vaccines licensed for use in Canada. Reporting no outcome of interest was also a reason for exclusion. Articles were excluded if they did not include data on seasonal trivalent influenza vaccine effectiveness, efficacy, safety, immunogenicity, reactogenicity, health-care seeking, absenteeism, missed days of work/school due to illness or economic impact. They were also excluded if the relevant data was solely contained in figures or tables where reliable point estimates could not be determined. In addition, secondary research articles were excluded, as well as articles that analyzed data that were already included in the review via another article. Lastly, studies were excluded if either the quality of

the article was rated as poor, if it contained insufficient information to assess its eligibility for the review or if it was a foreign language article that could not be reliably translated and assessed in English. Based on these criteria 184 articles were excluded upon full-text review (Figure 1).

All 67 eligible articles were data abstracted using a common abstraction form which had sections that were tailored to the potential biases in randomized controlled trials (RCT), case-control, cohort and cross-sectional studies, as well as sections for each of the outcomes of interest. The outcomes abstracted included laboratory-confirmed influenza infection, influenza-like illness, serologically-confirmed influenza infection, immunogenicity, absenteeism, health-care seeking, reactogenicity, adverse events and serious adverse events. Furthermore, the data abstraction form was designed to capture relevant sub-group analyses; for example, on different vaccines, influenza seasons or age groups. The data was abstracted into the forms as reported by the article's authors. However, some fields were calculated based on data presented in the articles. This was primarily for articles that did not report the fields or effect measures of interest (e.g. relative risk, odds ratios, vaccine effectiveness, GMTR) but reported the raw data needed to calculate these effect measures. All included data abstractions were assessed for quality control and the results were compiled for the present systematic review.

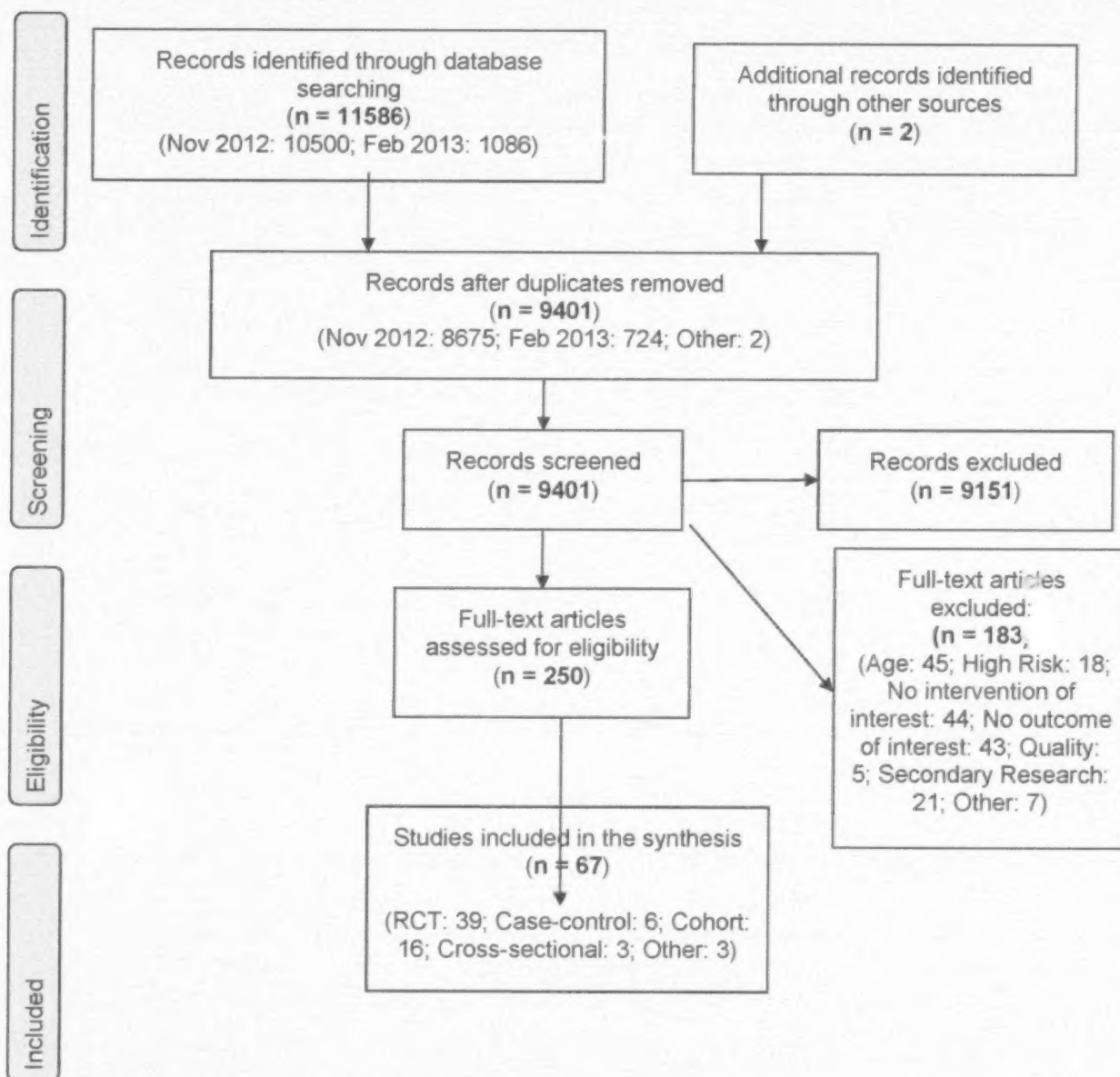
Table 1. Influenza vaccine systematic literature review search strategy

DATABASE		Web of Science	Medline	EMBASE
KEYWORDS AND LIMITS	DISEASE	influenza OR flu OR h1n1	influenza.mp. or exp Influenza, Human/	influenza.mp. or exp influenza/
		AND	AND	AND
	INTERVEN- TIONS	vaccin* OR immuni* OR innocul*	influenza vaccine.mp. or exp Influenza Vaccines/	vaccine.mp. or exp vaccine/
		AND	AND	AND
	OUT- COMES	effective* OR efficacy OR outcome OR response OR h\$emagglutinin OR antibod*	[(vaccin* or immuni* or innocul*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]] OR [(effective* or efficac* or outcome or response or hemagglutinin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]] OR (safety or adverse or side effect or precaution or tolera* or toxicity or guillain barre or neurologic* or signal or contraindicat* or complication or undesirable or fail* or mortality or death or hospital*).mp. [mp=title,	(vaccin* or immun* or inoculat*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] OR (effective* or efficac* or outcome or response or hemagglutinin or haemagglutinin or antibod*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] OR (safety or adverse or side effect or precaution or toler* or toxicity or Guillain Barre or contraindicat* or signal or neurologic* or Bells palsy or complication or undesirable effect or fail* or mortality or death

DATABASE	Web of Science	Medline	EMBASE
	neurologic OR Bell's palsy OR contraindication OR signal OR complication OR undesirable effect OR failure OR mortality OR death OR hospital* OR concomitant OR parallel OR concurrent OR collateral OR joint OR coincident	abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] OR (concomitant or parallel or concurrent or collateral or joint or coincident).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] OR antibod*.mp. or exp Antibodies/ or exp Antibodies, Monoclonal/	or hospital*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] OR (concomitant or parallel or concurrent or collateral or joint or coincident).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
	AND	AND	AND
POPULATION	human*	Limit to humans and "all adult (19 plus years)"	Limit to human and adult 18 to 64 years
	AND	AND	AND
TIME PERIOD ^a	2000-01-01 to 2013-02-05	Limit to 2000-Current (February 5, 2013)	Limit to 2000-Current (February 5, 2013)

Web of Science databases searched = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH. 1) November 9, 2012 with the time period: 2000-01-01 - 2012-11-09 [Web of Science] and 2000 to current [Medline and EMBASE]. 2) February 5, 2013 with the time period: 2012-11-09 – 2013-02-05 [Web of Science] and 2012 to current [Medline and EMBASE]

Figure 1: Systematic Review Process Flow Diagram - Influenza vaccine effectiveness, immunogenicity and safety in healthy adults 19-64 years old



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